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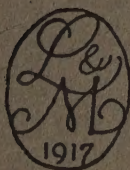
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E. BUSCH:
STUDIES ON THE NERVES OF
THE BLOOD-VESSELS
WITH ESPECIAL REFERENCE TO PERIARTERIAL
SYMPATHICECTOMY



SUPPLEMENTUM II
LEVIN & MUNKSGAARD · KØBENHAVN

MCMXXIX

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Konsistorium, den 21. November 1927.

Beckingsdale

I have been thinking of you very much lately, and wondering how you are getting on. I hope you are well and happy.

I have been very busy lately, but I have managed to find some time to write to you. I have been thinking of you very much lately, and wondering how you are getting on. I hope you are well and happy.

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STUDIES ON THE NERVES OF THE BLOOD-VESSELS
WITH ESPECIAL REFERENCE TO PERIARTERIAL
SYMPATHICECTOMY

Forsvaret finder Sted Torsdag d. 6. Februar 1930
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STUDIES ON THE NERVES OF THE BLOOD-VESSELS

WITH

ESPECIAL REFERENCE TO PERIARTERIAL
SYMPATHICECTOMY

BY

E. BUSCH



LEVIN & MUNKSGAARD PUBLISHERS

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Denne Afhandling er af det lægevidenskabelige Fakultet antaget til offentlig at forsvares for den medicinske Doktorgrad.

København, den 29. Juni 1929.

*C. E. BLOCH,
pro dec.*

Printed in Denmark.

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KØBENHAVN

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E. B.

The present work was finished from my hand in
August 1928.

E. B.

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INTRODUCTION

THE interest in the innervation of the blood-vessels from a surgical point of view has in recent years been largely increased by the modern surgery of the sympathetic and especially by periarterial sympathicectomy. It seems more and more probable that the theoretical basis of this operation is wrong, and that due regard has not been paid to the existing anatomical and physiological evidence. It is then only natural that the examination of these problems has in recent years been conducted with vigour especially in surgical quarters, but it seems remarkable that these investigations have led to rather conflicting results, especially in the sense that modern investigators have not been able to confirm previous workers' discovery of nerves in the vascular wall.

On the other hand, some surgeons not only think that nerves are present in the walls of the blood-vessels, but even that *peripheral nerve-centres* are to be found there; the modern advocate of periarterial sympathicectomy, *R. Leriche*, has made a complete *volte-face* as to these problems; while the original basis of periarterial sympathicectomy as he expounded it was the complete degeneration of the nerves of the blood-vessels by this operation, he declares in 1927, that the only possible explanation of the fact that vessels, which he has isolated from the nervous system, are still able to adapt themselves to the varying temperature, must be the existence of peripheral nerve-centres ("— *il reste que l'innervation motrice des vaisseaux est assurée avant tout par des centres périphériques, intramuraux, comme celle des intestins et du coeur*").

As yet we are far from a complete understanding of these relations, nor do the interpretations of the existing facts agree. While some workers think that the contraction of the muscle of the blood-vessels is due to nervous stimuli and that it would be unphysiological to suppose a normal muscle-cell working without stimuli or control from the nervous system, other investigators think that the nerves of the *muscularis* of the blood-vessels, even if they exist, are of slight importance in so far as the control should be sought for in the protoplasm of the muscle-cells themselves.

In anatomical quarters it has recently been asserted that the *muscularis* of the blood-vessels should be without nervous elements at all, because these workers have not been able to demonstrate such nerves

histologically. On the other hand some physiologists make it extremely probable, solely on physiological evidence, that these nerves *do* exist — some even seem able to draw conclusions as to their morphological arrangement (*A. Krogh*).

But even if earlier histologists' discoveries of nerves in the walls of the blood-vessels may seem a sufficient guarantee of the existence of these nerves, the question arises: *What functions do these nerves perform?* And with especial reference to periarterial sympathectomy we must ask: *By what means and in what direction may the function of these nerves be influenced?*

As previously mentioned, the understanding of the importance of these problems now seems to have been awakened. Thus *Colmers* declares in 1925: "*Die Sympathicuschirurgie wird erst dann ihre volle Berechtigung gefunden haben, wenn sie fassen wird auf klar erkannten physio-pathologischen Vorgänge*" — and numerous surgeons throughout the world think it their duty to await further anatomical and physiological evidence before they care seriously to consider periarterial sympathectomy.

So far we must admit that we do not fully understand these problems, and that the existing facts may be interpreted in various ways. To contribute something to the understanding of these questions has been the object of the present work.

An investigation which aims at elucidating these problems should be of *anatomical* as well as of *physiological* nature. In the first place the nerves of the blood-vessels, the existence of which some modern histologists deny, must be demonstrated, and their morphology studied. But inasmuch as it may not be possible, by these means alone, to draw safe conclusions regarding the nature of these nerves, it is necessary to ascertain by physiological experiments to what part of the nervous system these nerves belong, where their trophic centres are situated, and which way (or ways) they follow to reach the blood-vessels.

This work, then, may naturally be divided into two parts: A *descriptive, anatomical* part, and an *experimental, physiological* part. While the first part of the task is to a certain extent accessible to investigation in man, the second part will have to be studied in animals. In order — if possible — to find a reasonable basis for applying the experimental results to man, it is absolutely necessary to ascertain whether the morphology of the vascular nerves in the animals employed and in man is so far identical that a comparison will not seem too improbable.

In the present work I shall then attempt:

10. Briefly to describe the morphology of the nerves of the blood-vessels in man and in the animals employed;

20. to determine whether these nerves are of sympathetic or somatic nature;
 30. so far as possible to determine what functions these nerves perform;
 40. to determine how — and if — these nerves become affected through certain operations which have been recommended as surgical therapy in man; and
 50. to discuss how far the results gained through this work may accord with the clinically observed effects of the same operations, the intended result being a better understanding of these problems.
-

I.

ANATOMICAL STUDIES ON THE NERVES
OF THE BLOOD-VESSELS

*Pour avoir une première idée des choses,
il faut voir ces choses. —*

Claude Bernard.

SURVEY OF PREVIOUS WORK IN THIS FIELD

Even as early as the 18th century several anatomists had dissected nerves on the blood-vessels (*Haller, Soemmering, Wrisberg*). These investigations, however, seem to the modern anatomist to be of more physiological than anatomical significance (see *Physiological Part*).

The first investigation, therefore, which shall be mentioned here, is that of *D. Lucae* of Frankfurt am Main (1809), who dissected branches from the nerve-trunks to the arteries; these branches ended partly in the periarterial tissue, partly in the muscular coat of the vessel. Concerning these nerves *Lucae* observes: "*Hingegen unterscheiden sich diese den Arterien eigenthümlichen Nerven schon durch ihre äussere Gestalt. Sie sind dünner, cylindrisch, schwer vom Zellgewebe zu unterscheiden, durchbohren das Zellgewebe der Arterie schräg und gehn geradesweges auf ihre Muskelhaut zu. Hier werden sie halb durchsichtig, breiten sich aus und legen sich in der Gestalt einer zarten Membran auf die Muskelhaut der Arterie. Hebt man diese Nervenhaut behutsam mit einer Pincette auf, so sieht man, dass sie eine strahlige Ausbreitung ist. Um diese Nerven zu Gesicht zu bekommen, muss man aus mageren und jungen Leichen, die vorher eingesprüsst sind, Bündel grosser Arterien und Nerven mit dem Zellgewebe ausschneiden und sie einige Tage in Brantwein legen*".

In contrast to the anatomists previously mentioned, *Lucae* thinks that these nerves are *not* arranged as slings around the vessels (*Haller*), and he is further of the opinion that these nerves are less numerous on small vessels, while previous investigators had asserted that the nerves were relatively more numerous on small arteries. Finally, some arteries, in *Lucae's* opinion, are totally destitute of nerves — *e. g.* the vessels of the brain.

Lucae further observes: „*Je jünger die Menschen sind, desto häufiger sind die eigenthümliche Nerven der Arterien, die zu ihrer Muskelhaut gehn; mit dem zunehmenden Alter werden sie weniger, so wie die Gefässe der Gefässe in ihnen weniger werden. Damit ist eine Abnahme des bildenden, wie des thierischen Lebensprocesses verbunden*".

Lucae's investigations were published as a dissertation and in Latin; it was, however, at the same time printed in German.

In Latin, too, is the next investigation to be mentioned: *Goering's Dissertatio inauguralis anatomica-physiologica de nervis vasa praeceque extremita-*

tum adeuntibus, Jena 1834. Goering mentions that Lobstein (1823) was not able to trace sympathetic nerves to the vessels, and confirms this for himself. On the other hand, Goering discovered nerves which reach the muscular coat of the vessels from the peripheral nerve-trunks. He then observes: „Ego in hanc tunicam (i. e. muscularis) nervulos sese immergere non vidi, sed tenues nervulos arteriis se affigentes observavi, quorum cylindri primitivi (Fontana) radiatim tunicae musculari adhaerentes, in ejus superficie terminantur, ita ut eorum actio in vasa non possit negari". This observation brings Goering abreast of some modern histologists, who — notwithstanding the modern technic — are not able to find nerves in the inner parts of the arterial wall.

About the same time the first of a series of investigations was published which were to become vitally important to the whole of neuro-histology, and which may not be passed by in silence, even if they did not especially aim at elucidating vascular innervation — viz. Remak's *Observationes anatomicae et microscopicae de systematis nervosi structura*, Berolini 1838.

Until that year only medullated nerves were known, and when Remak pointed out that he had discovered "nerve-fibres" in the sympathetic system which were non-medullated, but provided with ovoid nuclei in their course, it cannot be wondered at that many of his contemporaries were extremely sceptical. Valentin asserted that the fibrils described by Remak were only fibres of connective tissue, and this interpretation prevailed for some time. Little by little other investigators became aware of the real interpretation, but as late as 1865 Kölliker doubted the nervous nature of the Remak-fibres.

In 1843 Remak communicated another observation, which is of the greatest importance in this connection: In the diaphragm of *talpa* he found "ein überaus dichtes Maschennetz von sehr zarten (unter 0,0015" starken) Nervenröhren — welche wegen ihrer Durchsichtigkeit an den unversehrten Bündeln der Beobachtung entgingen. Solche feine Röhren sehe ich in grosser Anzahl, wenn auch nicht in so dichten Maschen verlaufend, in den Muskeln aller Wirbelthiere neben den bekannten stärkeren Röhren, denen bogenförmige Umbiegungen Valentin als Endschlingen betrachtet".

As might have been expected, these revolutionary discoveries met with great opposition from a number of histologists. It is therefore only natural to mention that as early as 1843, a Danish investigator, Hannover, was able to confirm the discoveries of Remak. Hannover saw fusiform nuclei along the course of these vegetative nerves and he was of opinion that they sometimes seemed to be lying beneath a fine, membranous sheath; and he remarks: "That the nerve-fibres form slings in the muscles and end in this way, I think may be taken for granted. They lie upon the muscular bundles, only in intimate contact with them, they do not penetrate into them, still less are they merged in their substance".

Remak and Hannover had seen these non-medullated nerves in striped muscle only. The Englishman Beale was the first to describe similar, net-forming fibrils in smooth muscle, first in the bladder of *rana*, later on in the blood-vessels. These fibrils, which Beale is able in his preparations to trace back to unquestionable nerves, are also accompanied by spindle-shaped nuclei, which Beale thinks consist of „germinative matter“, and he declares that these nuclei are characteristic of these nerves. The fibrils are about 1/1000 inch (*i. e.* about 25 μ) thick. Beale (and after him Ciaccio) used quite simple methods of preparation, later, however, he employed impregnation with chromic salts. In striped as well as in smooth muscle Beale only found nerve-nets as the ultimate endings of the nerves, and this holds good, too, of the nerves in the muscular coat of the blood-vessels: “— not only are nerve-fibres distributed in considerable number upon the external surface of the artery, ramifying in the connective tissue, but I have also followed the fibres among the circular fibres of the arterial coat. — — — These nerves invariably form net-works with meshes”.

In 1864 Ciaccio, by Beale's methods, came to exactly the same results; he saw very fine nerves with “spindle-shaped swellings”. He asserts that “the capillaries of the skin of the frog are largely supplied with nerves. In the finest arteries and the largest capillaries the nerve-fibres run parallel and close by them, but in the finest ones, the nerve-fibres after running with them some distance, generally cross them and pass from one capillary to another. The nerve-fibres distributed to all capillaries are in connection with one another, so that they form a lax plexus, which lies on different planes”. Their illustrations show beyond all doubt that the fibres which Beale and Ciaccio describe really are nerves. In the bladder of *rana* Beale was able to demonstrate ganglion-cells in connection with the nerves, while Ciaccio found no such cells in the skin of the frog.

Believing that no muscular cells were to be found on the walls of the capillaries, Beale was of opinion that the nerve-plexus surrounding them might be of an afferent, sensory nature, and in 1872 he declared that the nerves of the capillaries were probably the first “sentinels” of the organism in its contest with injuries; he observed that, when he stimulated the web of the frog, it might happen that small vessels, far from the place of stimulation, responded by contraction. That this contraction was due to impulses transmitted through nerves, Beale had no doubt. As the existence of muscular cells on the wall of capillaries was unknown to him, Beale sought to explain how this contraction was brought about by assuming that the numerous “bioplasts”, which he found around the capillary wall, by absorbing water and salts were brought to protrude into the lumen of the vessel, thereby obstructing or checking the flow of blood — a theory which is defended even today.

In the period in which the investigations of Beale were performed, how-

ever, several other investigators worked at the same problems, and when *Beale* is mentioned first, it is because he was without doubt the first to assert the presence of *Remak*-fibres on the blood-vessels.

In Germany *Kühne* and *Kölliker* had at the same time thought they could substantiate that the nerves of smooth muscle terminated in free endings. In 1862 *Kölliker* describes these endings as „freie, verschmälerte Ausläufer“ very seldom communicating with each other and ending in small „Endknospen“ exactly as described by *Kühne*, the difference between the two investigators being that *Kühne* finds them internal, *Kölliker* external to the sarcolemma. On the blood-vessels *Kölliker* saw the same „blasse Fasern“, which he describes in striped muscle, and he saw these fibres accompanying the vessels for long distances, but he makes no special mention of their endings, and he does not venture to express any opinion of their nature (motor or sensory). With *Beale* *Kölliker* had a heated controversy, as he asserted that *Beale*'s „nerves“ were connective tissue-fibrils (*Kölliker* made the same objection to the *Remak*-fibres), but *Beale* was not at a loss for a reply („Professor *Kölliker* seems to conclude in too many cases, that what he has failed to see, does not exist“).

About the same time *His* also occupied himself with the nerves of the blood-vessels; in 1863 he declares that *Arnold*, *Langhans*, *Recklinghausen* and *Sämisich* have confirmed *Kölliker*'s (1862), *His*'s and *Billroth*'s discovery of reticular nerves on the vessels, and *His* for his part is able to confirm *Arnold*'s demonstration of reticular motor nerves. *His* was working with the blood-vessels of the frog's mesentery and the dog's bladder; he prepared his preparations with acetic acid and he was able to see medullated nerves passing to the vessels; the neurilemma is continuous with the adventitia of the vessels, while the nerve itself continues its course into the vascular wall „marklos mit den bekannten Längskernen“. The nerves often divide dichotomously, and in the place of division a small triangular swelling is often to be seen; the finest nerves are 1/1000" thick and are placed deeply in the adventitia and in the muscularis.

In 1864 one of the pupils of *Kölliker*, the Dane *Jens Christian Lehmann*, in a much quoted paper records the first discovery of ganglion cells on the walls of the blood-vessels. *Lehmann* worked with acetic-acid-preparations, which were examined in glycerine and in the wall of the *vena cava* (rat) he discovered „verästelte, feine Nerven mit Längskernen“, but they do not form any complete net-work. In connection with the nerves he found numerous collections of ganglioncells in the abdominal part of the vein — 0.021—0.126 mm. in diameter, but he had to concede that he could not find similar cells in the walls of any other vessel; this, however, he thought due to „Missgeschick“. In the wall of the aorta, on the other hand, *Lehmann* was able to demonstrate a plexus of pale, in part nucleated, nerves.

A few years later (1866) *Bidder* found similar ganglioncells on the

blood-vessels of the submaxillary gland in dogs, while *F. Darwin* (1874) was able to follow nerves from the ganglia in the frog's bladder to the vessels of the bladder-wall.

Combining the discoveries of the various investigators at this time, the following nerve-elements had been demonstrated on the blood vessels: *Medullated nerves* (known for a long time); *nerve-nets of non-medullated nerves* (*Beale* 1860) and *ganglion-cells* (*Lehmann* 1864); the non-medullated nerves had been first seen by *Remak* in 1838 in striped muscle as nerve-nets (ultimate endings), and *Hannover* had confirmed his discoveries in 1843.

However, as previously mentioned, several other investigators had formed the opinion that the nerves in smooth muscle end in *free terminations*, and this point of view gained numerous partisans in the following years, and the contest between the two conceptions has not yet been brought to a close.

One of the first workers who embraced *Beale's* interpretation was *Kessel*, who in 1868 examined the *membrana tympani*; he found a "*Grundplexus*", from which numerous fibres passed to the vessels on which they formed a rich plexus continuing on to the capillaries: „— *so sehen wir einzelne Nervenfasern sich den Capillarconturen dicht anschmiegen, auch wohl stellenweise wieder von denselben abheben, so dass ein schmales helles Raum zwischen Nerv- und Gefässwand sichtbar wird*". *Kessel* mentions that the nerves of the capillaries may end in a "*birnförmig Anschwellung*", but these may also be seen at the points of division, and he therefore thinks: "*Es ist sonach kein Anhaltspunkt, die Anschwellungen als die letzten Enden von den Gefässnerven zu betrachten*".

Klein, too, (1870—1872) could agree with *Beale* — but with some reservation. *Klein* worked with the *membrana nictitans* of frogs, but employed a different method of preparation (chloride of gold and tartaric acid). *Klein* asserts that *Beale* only saw the coarser non-medullated nerves on the vessels (*Klein's* "nerves of II order") and these nerves, in *Klein's* opinion, are only *accompanying* nerves to the capillaries. From these fibres finer, more granulated nerve-fibrils (*Klein's* "nerves of III and IV order") pass to the walls of the vessels and here form a rich plexus on the capillary-wall ("*surrounds the capillary like a kind of nervous sheath*"), but *Klein* himself writes: "*I was never able to find such a thread connected with the vascular wall*". Later on he examined the larger vessels in the mesentery of frogs, and found coarser, non-medullated fibres in the adventitia, but "*with respect to the nerves of the inner vascular wall I cannot make any assertion worth recording*".

Nor can *Tomsa* (1869) make any certain statement with regard to the endings of the nucleated nerve-nets which he finds on the capillaries in the human skin. Nor does *Popoff* with his preparations of nerves (?) on the capillaries of the liver, venture to put forward any explicit statement.

As mentioned above, *Kölliker* was the first who, in contrast to *Beale*, saw *free nerve-endings* in smooth muscle, and a number of later workers have confirmed and extended this discovery. While *Kölliker* did not venture to say just *where* the nerves terminate in relation to the muscle, *Klebs* (1863) was able to see $1\frac{1}{2}$ —2/10.000 mm. thick (!) nerve-fibrils pass to the muscle-cells, and merge with their substance — a similar arrangement to that described by *Trinchese* in striped muscle. *Engelmann* and *Tolotschinoff* (1869) arrive at the same result, *Engelmann* by observations on the wall of the ureter, *Tolotschinoff* by work on the bladder of frogs.

Frankenhäuser (1867), *Lippmann* and *Hertz* (1869) went still further. *Frankenhäuser* examined the uterus and found that the finest non-medullated nerves, after repeated dichotomous division (at the point of division he often saw a little node), penetrated into the muscular cells and ended in free terminations in the nucleolus itself.

Lippmann, however, in the mesentery of frogs (gold-impregnation), saw medullated as well as non-medullated nerves pass to the vessels, there forming a "*relatives weitmaschiges Netzwerk rings um das Gefässrohr*" ("*Primär-plexus*"), from which nucleated, 0.006—0.008 mm. thick fibrils penetrated into the vascular wall and formed a plexus in the adventitia; upon the tunica media itself the nerves ran parallel to the muscular cells; from this plexus, thin varicose fibrils ran in between the various muscle-cells, here forming an intramuscular plexus and from this "*Endfäschen*" passed "*in die Muskelkerne*". On quite small arteries, too, *Lippmann* found nerve-nets; on the capillaries he saw 1—2 thin, pale fibres, which were united with each other through oblique anastomoses — or he saw one single fibre, surrounding the capillary in a long spiral. Ganglioncells *Lippmann* only saw on the vena cava, never on peripheral vessels. Later on he examined the mesentery of guinea-pigs and rabbits and on the whole found identical conditions.

Hertz examined the nerves in soft myomata of the uterus, and he, also, found free nerve-terminations in the nuclei of the muscle-cells. —

While, then, some investigators find reticular, *pericellular* nerves as the ultimate nerve-terminations, other workers describe *intracellular* — nay, *intracellular* free nerve-endings. *Arnold*, whose work was done in about the same years, takes an intermediate stand-point: He thinks that the nerves end in the nuclei, but he is also of opinion that a sort of plexus is formed, the nerve perforating the nucleus and anastomosing with a similar fibril on the other side of the nucleus. The nerves of the blood-vessels *Arnold* found arranged in a *fundamental plexus* in the adventitia, in which he saw scattered ganglioncells, and in an *intermediary plexus* in the intermediary zone between the adventitia and the media; from this plexus the fibres pass into the muscularis to the *plexus intramuscularis*.

Krause is somewhat reserved with regard to the findings of most previ-

ous workers and thinks that the greater part of their "nerves" is simply connective-tissue — an opinion for which we cannot blame him when we consider the rather primitive methods of preparation of most of these investigators. When, however, the illustrations of these early workers are studied, no doubt can exist but that many of these men really saw nerves, and one is compelled to admire the results obtained with such imperfect methods.

In these years work on the vascular innervation was also done in France. In an extensive work on the structure of the arteries (1865) *Gimbert* remarks that he has never seen free nerve-terminations in human preparations; on the other hand, both he, and before him *Robin* (1864) and *Ordonnet*, have seen such on the vessels in the palate and the mesentery of frogs. *Gimbert* has also seen ganglioncells on the vessels: "*Ces ganglions sont le point de départ des nerfs, qui vont se perdre sur les vaisseaux*". The nerves of the capillaries are "*réduites à l'état d'élément de Remak isolé et disparaissent en pointe au milieu de la masse*". On the quite small capillaries he does not, however, see nerves, but only sees them just so far as the muscular cells go, and he concludes: "*Il est donc évident, que tout ce qui a force impulsive dans les arterioles et capillaires est sous le dépendance du grand sympathique. Reste à démontrer le fait pour les gros vaisseaux, et il est probable, qu'il est analogue*".

While *Gimbert* does not express himself explicitly as to the ultimate ends of the nerves, *Hénocque* (1870) finds that the nerves of the vascular wall, after having formed a "*plexus intermédiaire*" in the more profound part of the adventitia, continue into the muscularis where they again form a continuous plexus; from this proceed "*fibrilles terminales*", which anastomose and "*se terminent par un léger renflement en bouton ou ponctiforme — plus souvent autour du noyau*". That these fibrils are really terminal, *Hénocque* thinks is supported by the fact that they are all of the same thickness and appearance in all the organs in which he finds them (bladder, bowel, vessels).

Both by dissection and for a smaller part microscopically *Frey* examined the nerves of the blood-vessels (1874—76), without, however, finding the slightest indication of nerve-nets; *Frey's* sketches from his preparations, however, make one suspect that he did not see real nerves. The same thing may be said of the illustrations of *Nesterowsky* (1875) and *Kolatschewsky*, which represent the nerves on the vessels of the liver — even *Nesterowsky* himself is not sure ("*Nie habe ich stricte Axencylinder gesehen*"). Nor could *Alexander* form any certain opinion of the nerves on the vessels of the *dura mater*, which he investigated by the gold-method of *Klein*.

In the great *Traité technique d'Histologie* (1875) *Ranvier* treats the question of the innervation of the blood-vessels. This eminent investigator also saw nerves on the vessels. In the adventitia he found "*un premier plexus*

à mailles larges et inégales, plexus fondamentale. Puis, à la surface externe de la tunique musculaire, ils se résolvent en un plexus à mailles étroites et assez régulières, plexus intermédiaire, qui jadis a été assez bien décrit par His d'après des préparations à l'acide acétique, et qui cet auteur a pris pour un réseau terminal. Le vrai plexus terminal ou plexus intramusculaire est formé de fibres beaucoup plus fines, qui se dégagent du plexus intermédiaire et qui très probablement fournissent des tâches motrices aux cellules contractiles de la tunique musculaire". In the "plexus fondamentale" Ranvier saw many medullated fibres — a fact none of the previous workers had stressed.

In the same year the first communication of Loewit appeared; in this the author published his first results with that method of gold-impregnation which came to bear his name, and which was for a time universally used. Loewit examined the nerves of smooth muscle and found them running in the interstitial substance between the muscle-cells, parallel to their arrangement. Everywhere he found a closed nerve-net (*"Ich hebe hervor, dass ich in meinen gelungensten Goldpräparaten immer nur zusammenhängenden Endfibrillen gesehen habe"*). Of the relations between muscle and nerve he remarks: *"Ein Zusammenhang zwischen Nerv und Muskel ist auf jeden Fall vorhanden, muss aber nicht in der Länge der ganzen Reihe statthaben; wo letzteres aber nicht der Fall, da ist der Zusammenhang immer in der Gegend des Muskelkernes vorhanden; — — — direct mit dem Kerne hängt die Endfibrille nie zusammen, sondern nur mit der Muskelsubstanz in der Nähe des Kernes. Von einer eigentlichen "Nervenendigung" in den glatten Muskeln kann also nach meinem Befund ohne weiteres nicht geredet werden"*.

On the capillaries, too, Loewit saw nerves; he, however, remarks: *"Für die schwächeren vermochte ich jener Nervenreichtum, namentlich jene von Klein beschriebene "nervöse Scheide" um die Capillarwand nie zu finden"*.

Nor was Gscheidlen able to find intracellular nerve-endings, and he almost embraces the interpretation of Klebs and Loewit in that he — like Goniaew (1875) — finds a double nerve-plexus in the vascular wall, a large-meshed one in the adventitia, and a finer terminal net in the muscularis; in the arteries the loops are narrower, in the veins wider. On the capillaries Goniaew saw a plexus of varicose, fine, nucleated fibrils, whose meshes were larger than the meshes of the capillary net itself; thus also this worker was not able to confirm Klein's "nervous sheath" round the capillary.

Meyer, who examined the nerves of the iris and the chorioidea in 1880, came to quite similar results; on the larger vessels he saw nerve-plexuses in the adventitia and on the media, but he was unable to follow them further. Lustig (1881), on the other hand, thought he found intracellular nerve-terminations merged with the nucleus of the cell in various animals.

Directly aiming at an investigation of the innervation of the blood-vessels Bremer (1872) examined frogs and lizards by Loewit's method, and found even the smallest capillaries encompassed by nerves, which were connected

through nodular enlargements with the vascular wall — but not with the nuclei; on smaller arteries *Bremer* found *three* nerve-nets, one in the adventitia, one in the intermediary zone, and one in the muscularis. The nerves of the vessels do not anastomose with other nerves in the surrounding tissue: "*Ein Nerv, der einmal an ein Gefäss herangetreten ist, verlässt derselbe nicht mehr*", and in *Bremer's* opinion this proves that the vascular nerves are not solely accompanying nerves.

Goldscheider, too, found that the nerves ran along the capillaries and were in very intimate contact with them; on the other hand, *Gruenhagen* and *Stirling & McDonald* — independently of each other — saw only non-medullated nerve-fibres arranged *around* the capillaries at some distance from them, while they never ran on the wall of the vessel itself. While *Gruenhagen* still speaks of a nerve-plexus of the capillaries, *Stirling & McDonald* saw only varicose nerves ("*like a string of beads*") running parallel to the capillaries, but "*as a rule they do not touch the wall of the vessel*". Like *Ranvier*, the two Englishmen found an outer plexus of *medullated* nerves on larger vessels, from which varicose, non-medullated fibres passed to an intermediary and an inner plexus in the muscular coat itself: "*It is most probable, that fine threads are given off, which end directly in the muscle-fibres of the middle coat, but this is not clearly proved*".

Similar results were obtained by *Geberg* in 1884.

A soberly written work, "*Die Nerven der Kapillaren*", was published in 1884 by *Krimke*, a practitioner in Hannover; he applied *Loewit's* method, as well as other gold-methods and examined the capillaries of frog, bat and man. Everywhere he found identical conditions: *All* capillaries are accompanied by non-medullated nerves, mostly two, which are united across the vessel by oblique anastomoses, less frequently by one nerve, which then twines round the vessel in a long spiral; *Krimke* did not find any nerve-net; on the contrary, he found free "*Endkörperchen*" everywhere on the capillaries, mostly triangular or fusiform, and seemingly connected with the vascular wall through a fine, fan-like plate. Sometimes a "*Hauptzelle*" may be interposed before the end of the nerve, but — judging from the illustrations — this formation seems to be identical with a *Remak's* nucleus, just as "*Endkörperchen*" no doubt corresponds to the previously mentioned nodes at the points of division. When *Krimke* did not see any nerve-net, this was without doubt due to the difficult and very capricious technic of gold-impregnation.

The year 1886 is a memorable year for neuro-histology, since it was in that year that *Ehrlich* published his first communications ("*Ueber die Methylenglaubeaktion der lebenden Nervensubstanz*") on a new, quite epoch-making method of nerve-staining, based on "*vital staining*". Here this method will not be treated exhaustively (see the chapter entitled "*Technic*"), but it must be mentioned that *Ehrlich*, from the very start, was able to

demonstrate a "reichliches Gefäßplexus um eine kleine Vene mit vereinzelt intensiv blau gefärbten Zirkulärmuskelzellen, die nach meinen Erfahrungen als Vasokonstriktoren *Har' ἔξοπῆν* anzusprechen sind". Ehrlich himself did not pursue his discovery in the neuro-morphological sphere, and it was reserved for a long succession of later workers to apply this new key to neuro-histological problems, and in *Russia* especially this new method was very generally adopted (*Arnstein, Smirnow, Dogiel* etc.).

During the following years the old contest of the nerve-terminations in striped as well as smooth muscle was renewed, elucidated by vital staining (*Aronsson, Feist, Fajnstajn, Gerlach, S. Mayer*), without, however, producing any new essential facts concerning the innervation of the blood-vessels.

In 1889 *Thoma* was, however, able to report that he had seen the nerves of the blood-vessels connected with undoubted sensory formations — viz. the *Vater-Pacini-corporcles*. Later on *Thoma* found these corpuscles in the adventitia of larger arteries, and his discoveries were confirmed by *Rattone* a. o. Before then *Beale*, and later *Kölliker*, had supposed that the nerves of the capillaries were of a sensory nature — in this period the existence of muscular elements on the capillary wall was not dreamed of — but it was only with the discovery of *Thoma* that it was reasonably safe to infer that the vessels did after all possess sensory nerves.

Only a few years later another form of sensory end-corpuscule was discovered on the vessels. This discovery is due to the Russian school which was inaugurated by *Arnstein* and carried on especially by *Smirnow* and *Dogiel*. In this period the Russians worked almost exclusively with the new methylene-blue-method, and we owe several of the most essential improvements of this method to them (see "*Technic*").

J. Dogiel examined the nerves of the myocardium with methylene-blue and chloride of gold and, like the previous workers, he found ganglioncells on the vena cava, but his investigations are quite dwarfed by the enormous production put forward by *A.S. Dogiel* in the years 1891—1909. One of the first works of *Dogiel* was on the terminations of the motor nerves in striped muscle, and he continued with investigations on the nerve-endings in the corpuscles of *Krause, Meissner* and *Herbst*. In 1893 he examined the nerves of the lacrymal gland, and makes brief mention of non-medullated nerves along the vessels.

Meantime another Russian, *Agababow*, (1892) had found the vascular nerves plexiformly arranged around the muscular cells, while *Smirnow* in 1895 communicated his discovery of an as yet unknown sensory nerve-termination in the myocardium. Here *Smirnow* first describes the "end-plates" ("*Endplatten*"), which were later on described by *Dogiel*, and which generally bear the name of this worker. These platelets *Smirnow* found as irregularly delimited formations, consisting of a finely-granulated plate, "*sensible Unterlage*", on which the nerve splits into irregular loops and platelets.

Smirnow thought that he could show by degeneration-experiments that these platelets were dependent on the depressor nerve, and he naturally concluded that the formations were *depressor-endings*.

Dogiel, however, was the first to describe these nerve-endings in the walls of the blood-vessels. *Dogiel* found them on smaller vessels in the heart of cat, dog and man as 0.05—0.3 mm. long, 0.03—0.08 mm. broad plates ("*Endsohlen*"), sometimes more convoluted; *Dogiel* emphasises that they always lie in *one* plane, often several over each other in different planes of the vascular wall, and he supposes that they are of importance for the regulation of the blood-pressure. Owing to the connection of the plates with *medullated* nerves, *Dogiel* concludes that their nature is *sensory*, also because they are somewhat similar to the sensory end-corpuscles in tendons (*Sachs, Rollett, Golgi, Cataneo, Kölliker, Ciaccio*). In the granulated substance, which forms the "*sensible Unterlage*", *Dogiel* sees peculiar, stellated cells.

Dogiel himself only describes these platelets on the smaller vessels of the heart; his pupil *Schemetkin*, however, found them in the aorta and the pulmonary arteries, and another of *Dogiel's* pupils, *Rachmanow*, (1901) confirmed *Thoma's* discovery of *Vater-Pacini*-corpuscles in the vascular wall (*aorta*).

As far as the motor nerves of the blood-vessels are concerned, *Dogiel* saw rich nerve-nets everywhere; another worker of the same school, *Ostroumow* (1895) found nerves loosely arranged in nets *around* the vessels in the papillae cutis, which nerves he, however, thought were vasomotor nerves. *Timofeev's* "vascular nerves" may, however, be doubted — in his illustrations they are suspiciously like cell-limitations.

In 1891 *Ramon y Cajal & Sala* had seen reticular nerves around the vessels, and their results were confirmed by *Ruffini, Sacerdotti* and *E. Müller*. On the other hand, *Bernheim* (1892) found *intracellular nerve-endings* in the smooth muscle of the frog's bladder, where he supposed he could see them terminate in a little "*Endfuss*". The American *Berkley* did not venture to say anything definite on the question, but he no doubt saw true nerves on the arteries in liver and kidney; these nerves were, on the smaller vessels, arranged in nets and provided with numerous "*ganglionic enlargements*", which, however, *Berkley* himself discovered to be only nuclei of *Remak* and the nodes at the points of division.

In 1894 at a congress *Ballowitz* demonstrated some preparations of peripheral, true nerve-nets (from electrical fishes) and was supported by *Eberth*; on the other hand, the existence of these nets was promptly denied by *Lenhossek*, who asserted, that "*alle Nervenfasern, motorische wie sensible, zentrale wie periferische, mit freien Endbäumchen auslaufen, ohne mit anderen Faserungsverästelungen oder mit Fortsätzen der im Bereiche ihrer Endigungen befindlichen Zellen, Anastomosen einzugehen*", and later, that "*die erste wirkliche Verbindung, die man zwischen zwei Nerven einwandfrei*

nachweisen könnte, der ganzen neuen Lehre vom Aufbau des Nervensystems verhängnisvoll werden musste". In connection with these declarations Merkel made the following remark at the same congress: "*Zahlreiche Untersuchungen über die periphere Nervenendigungen haben sicher erwiesen, dass an der Endstelle Netze vorkommt, welche von mehreren Nervenfasern versorgt werden*".

Lenhossek, however, is not alone in his opinion; thus Jacques (1894) asserts that the vascular nerves, which he examined with methylene-blue, are characterised by just this feature that they *never* anastomose with each other, and that they end in free, bud-like terminations; Heymans & Demoor formed the same opinion after impregnation *a. m. Golgi*; these investigators found, moreover, that the nerves end in "*un renflement à leur extrémité*".

It seems, however, that Heymans & Demoor have also seen plexiform nerves on the coronary vessels; they express themselves more definitely against the intracellular nerve-terminations: "*L'excitation nerveuse motrice, amenées par ces fibres terminales, agit par contact sur la substance contractile*".

Concerning the capillaries Heymans & Demoor come to the conclusion that they do not exhibit any sign of possessing nerves at all.

Nor is Barbieri, who uses the same impregnation-method on dogs, able to see any anastomoses between the vascular nerves; on the other hand these nerves often form a network ("*réseau*"), from which they pass on to their terminations in the media, where "*la terminaison de chaque fibre est indépendante — par des extrémités libres renflées en boutons*". He never sees ganglion-cells on the vessels.

Bietti, Bethe and N. Schmidt, however, adhere to the peripheral nerve-nets, and Bethe, moreover, thinks he can see peripheral nerve-nets *with* ganglion-cells, where the net is formed by short anastomoses between the cells. Probably Bethe was wrong in this question — as shown by several later investigators — and the whole of his ingeniously constructed theory of the arrangement of the nervous system is thereby doomed. That Bethe's discovery has been interpreted in a new way in our day will be mentioned later.

In 1895 Gad communicated a new method of nerve-staining with hematoxyline and saw plexiform nerves on the vessels even on the capillaries, while in the same year P. Schultz saw the same free, bud-like nerve-terminations as E. Müller: "*Die Endvaricositäten, womit der Nerv endigt, legt sich auf den Zellkörper selbst, berührt denselben, senkt sich aber nie in denselben ein*".

In Scandinavia, too, important contributions were made in this sphere through the excellent work of G. Retzius. This worker used most of the known methods of nerve-staining, especially methylene-blue, and published

his results in the sumptuously produced "*Biologische Untersuchungen*". His work on the motor nerve-terminations (molluscs and frogs) appeared in 1892, and here he finds the same conditions as *Kölliker*, the nerves ending in free, bud-like terminations, which lie outside the muscle-cell just opposite the nucleus — "*ein Eindringung der Nervenäste in die Substanz der Muskelzellen, respektive eine Verbindung mit dem Kern, ist an den vorliegenden Präparaten nie zu sehen und auch wohl keineswegs anzunehmen*". With impregnation, too, *Retzius* studied the vascular nerves, which also in the spleen and kidneys have free terminations (*cf.* a beautiful, but somewhat diagrammatic (?) drawing in that work (*Fig. 1, Tafel XXI*)).

Retzius is also able to confirm *Smirnow's* free, sensory endplate, and he thinks that the sensory nerves, too, have free terminations — they do not even anastomose, which the motor and vascular nerves often do. Even if *Retzius* admits a certain plexus-formation, he most definitely denies the existence of the peripheral "*Endnetze*".

Apathy — contrary to *Retzius* — finds free, intracellular nerve-endings; these may again leave the muscle-cell, but this eminent investigator, too, doubts the existence of peripheral nerve-nets.

Due to the work executed in the years 1880—1890, nerves have been found on most of the vessels in various animals; one might be tempted to describe these years as the golden age of neuro-histology, for hardly ever, before or since, has there lived at the same time such a number of prominent investigators in this field.

Some few vessels, however, remained, for which the existence of vascular nerves was doubted, *viz.* the vessels of the *lung* and of the *brain*, and this doubt was supported by various physiological investigations.

As far as the *lung* is concerned it is only very near our own time that vascular nerves have been demonstrated, while as early as the nineties it was asserted that the *cerebral vessels* were provided with nerves; in 1897 *Obersteiner* was able to confirm this in a small paper, while *Morrison* and *Huber*, independently of each other, came to the same result in 1899. The work of *Huber* is the most extensive; he used methylene-blue and saw medullated nerves (which he supposed to be *sensory*) as well as non-medullated nerves (which he assumed to be *sympathetic, motor* nerves) on the cerebral vessels. The latter nerves were plexiformly arranged in the adventitia and in the intermediary zone between the adventitia and the media, while the nerves in the muscularis itself ran parallel to the muscle-cells and "*terminate in fine granules on the muscle-cells*". Some degeneration-experiments, by which *Huber* hoped to examine more closely the nature of these nerves, failed, and were not continued.

In 1900 *Hunter* was able to confirm *Huber's* observations, while *Rohnstein* could not find any nerves at all on the cerebral vessels, either by the

hematoxyline-method of *Gad*, by *Golgi's* method, by *chloride of gold*, by *methylene-blue* or by a combined *osmium-methylene-blue-staining*, and he therefore concluded that the nerves demonstrated by all other authors were "*Vortäuschungen*".

On the vessels in the *dura mater*, *Wreden* (1906), on the other hand, saw sensory nerves with *Smirnow-Dogiel's* end-plates.

Siebler examined the nerves of smooth muscle using *Gad's* method. He saw nerve-nets which surrounded the muscle-cells, but found it improbable that every single cell should be provided with a special nerve. The nets are stressed by *Siebler*: "*In the muscular and glandular tissue — and perhaps throughout the body — there is a vast peripheral nervous plexus belonging to the capillary blood-vessels. The nerves of the capillaries, which may perhaps be regarded as nutritive nerves, regulate the production and transsudation of lymph, and are concerned in the mechanism of glandular secretion. They may be called into activity both by peripheral influences and by impulses received from the central nervous system and the sympathetic ganglia; they may influence, through their connections with the vaso-motor nerves on the arteries and the veins, the blood supply of a part*". Thus *Siebler* cannot imagine that the capillary nerves are motor nerves, in spite of *S. Mayer* simultaneously having confirmed *Rouget's* demonstration of *contractile cells on the capillaries*.

In the same year *Kytmanow* found for the lymph-vessels that, even if several nerve-nets were formed in the vascular wall, the nerves at last ended in free terminations, intracellularly in the muscle-cells; *Kytmanow* likewise found free sensory nerve-endings in the walls of the lymph vessels. Judging by the drawings of *Kytmanow*, *Dogiel* seems to be right in his assertion that these vessels are less plentifully provided with nerves than the blood-vessels; *Dogiel* also maintained that the nerves on the lymph-vessels run more parallel to the course of the vessel, while on the blood-vessels they take a more circular course.

In 1901 there appeared a communication on the cutaneous nerves, by *Leontowitsch*; he used a modified methylene-blue-staining (see *Technic*) and incidentally mentions plexiform nerves on the cutaneous vessels. *Dogiel* (1903) investigated the same problem; while *Ruffini* thought that the cutaneous nerves originated from the vascular plexuses, *Sefameni* asserted that these nerves were independent, *sensory* nerves, and this *Dogiel* approves, conceding that the sensory "*Grundgeflecht*" in the subcutis follows the course of the vessels. In the skin, too, *Dogiel* demonstrated *Smirnow's* sensory endings, an observation, which *Ceccherelli* and later *Heidenhain* confirmed.

An Italian, *Tricomi-Allegria*, also occupied himself with the nerves of the capillaries (1904) and he states that the nerves end in free terminations: "*I plessi vasali non si limitano ad accompagnare le pareti delle vene e delle arterie, ma si prolungano sui capillari. Sia che questi si esaminino in*

sezione trasversa e sia anche in sezione longitudinale, si vedono chiaramente delle fibrille nervose scorrere non solo in mezzo alle cellule endoteliali, ma anche penetrare dentro di queste, dove descrivono delle curve, delle ansa più o meno vicine al nucleo". He gives a few pictures, and in one of these is to be seen "*capillare sanguigno, fillette nervosi perivasale, filetti inter- ed intracellulari*".

While Agababow's "vaso-motors" in the sclera are to be accepted with reservation, an excellent work on the vascular innervation by *Lapinski* appeared in 1905. This communication — like all the works of this investigator — is distinguished by its thoroughness. *Lapinski* examines (with methylene-blue) the nerves of the blood vessels in young dogs and finds the following conditions: *In the perivascular tissue* plexiform medullated and non-medullated nerves are to be seen. From this plexus branches pass to the *adventitia*, where a broad-meshed plexus with medullated and non-medullated fibres is formed; here, moreover, are to be found nerve-endings of the appearance of "*Trauerbirke*", "comets' tails" and "ivy-branches". In the inner part of the *adventitia*, right *on the muscularis*, a nerve-net of naked nerve-fibres, in part isolated, in part collected in bundles is often to be seen, and from this branches pass *into* the *muscularis* itself, in which, in addition, one or two nets are formed; here the fibrils are thinner and often varicose.

Concerning the ultimate terminations of the nerves, *Lapinski* does not pronounce any opinion; in the same year *Mangold*, on the other hand, also with methylene-blue, finds free nerve-endings in the sarcoplasm in muscle-cells of *crustacea*, and *Retzius* sees free motor nerve-endings on the muscle-cells in the blood-vessels of the *chaetopod*; however, since he also finds these "terminations" on the vascular wall *between* the muscle-cells, he mentions the possibility, that the "terminations" might be due to incomplete staining. With silver impregnation *Retzius* also obtains the same result, while next year *Botezat* finds a *completely closed nerve-net* in the vessels of the oral mucous membrane of birds. *Botezat* is of opinion that this net is sensory; on a few occasions he, too, sees the "comets' tails", described by *Dogiel*, *Lapinski*, *Retzius* a. o., but he supposes that these are due to incomplete staining of the nerve-net. In addition to this sensory net, which pervades the whole of the vascular wall, *Botezat* sees every single muscle-cell surrounded by a closed nerve-net, which he assumes to be entirely motor; on the capillaries, too, he finds reticular nerves.

During the following years several investigators worked zealously at the problem of the innervation of the blood-vessels, and in 1906 weighty communications by *Ioris*, *Lapinski* and *Leontowitsch* appear.

As mentioned above, many held that the existence of true, peripheral nerve-nets was a menace to the whole *neurone-theory*, and it is no wonder that many began to doubt; thus in 1903 *Ioris* writes "*Le théorie des neurones*

est basée sur une série de véritables dogmes rigides et inflexibles; mais aucun d'eux n'est scientifiquement prouvé" and later on "le neurone n'est pas un centre fonctionnel. Ce rôle semble souvent revenir au réseau fibrillaire, qu'il soit intra- ou extracellulaire", and in 1906 he published his investigations on the innervation of the blood-vessels, in which the nerve-nets are of the greatest importance: The sensory as well as the motor innervation takes place from a joint "*plexus nerveux ganglionnaire périvasculaire (mixte sensitivo-moteur)*", in which there are numerous medullated nerves; in addition to this plexus a few "*fibres satellites*" are to be found external to the vessels, and these end elsewhere, but for the vascular nerves themselves it holds good that they "*ne s'anastomosent qu'entre eux et jamais avec autres nerfs musculaires, glandulaires etc. environnants*". In the perivascular plexus numerous ganglion cells with a little nucleolus and provided with Nissl-granules are to be found. From this plexus "*fibres motrices*" go to the "*plexus fondamentale*", which is exclusively motor and is placed in the innermost part of the adventitia; on arteries larger than 0.15 mm. in diameter, an additional net is formed at the limit between the adventitia and the media, and from this branches pass to the "*plexus intramusculaire*", which has irregularly formed meshes, mainly running parallel to the axis of the vessel. The ultimate ends of the nerves Ioris finds as a closed net of "*neuro-fibrilles*" — quite thin fibrils which originate in the "*plexus intramusculaire*" and which run around and between the individual muscle-cells, in all cases *pericellularly* only. As the diameter of the vessel diminishes, the nerves become less numerous, and on arteries with only *one* single layer of muscle-cells, only *two* plexuses are to be found viz. the *adventitial* plexus and the *intramuscular* plexus, from which the neuro-fibrils originate.

The sensory nerves issue from the joint "*plexus périvasculaire*" and do not subsequently join in the formation of nerve-nets in the inner parts of the vascular wall, but mostly end in free terminations with a "*plaque sensitive*", corresponding to the Smirnow-Dogiel platelets — mostly in the adventitia, seldom in the media, *never* — as asserted by Kytmanow and Jacques — in the intima. The *capillaries* are provided with single "*neuro-fibrilles*", but Ioris sees numerous capillaries without such an innervation; the meshes in the nerve-net are larger than the meshes of the capillary plexus itself, and the individual fibrils seem in places to break up into *little local plexuses*, the fibrils here being extremely thin.

The same year Lapinski discusses his earlier work on the innervation of the blood-vessels of the dog's hind leg, and adds some remarks on the regeneration of the vasomotor nerves, which he thinks takes place very slowly, if at all. In addition he speaks of *the changes of the vessels* following upon section of the vascular nerves. He finds the vessels partly dilated and tortuous, partly varicose and obliterated — this last due to proliferation of the intima. Lapinski was in no doubt that these phenomena were due to the

section of the vascular nerves, but to what function of the nerves the changes are due, he cannot say; he thinks that the increase in the amount of blood present in the extremity after the operation, in connection with the loss of elastic tissue which he describes, causes the degeneration of the vascular wall (*see Physiological Part*).

As to the ganglion cells, which *Ioris* a. o. had seen upon and in the vascular wall, after *Lapinski's* degeneration experiments the existence of such cells seems very doubtful (*see Physiological Part*).

Leontowitsch discusses the question of the existence of peripheral ganglion cells on the vessels in his work on the vascular innervation in *rana esculenta* (1906), and even he finds numerous, though somewhat "*eigenartige*" ganglion cells on the vessels; he is not beguiled into admitting the nuclei of *Remak* as ganglion cells, but "*neben den beschriebenen Netzen Remak'scher Zellen besitzen die Gefäße eine grosse Menge echter Ganglienzellen*", which contain *Nissl*-granules and which in several respects seem characterised as true ganglion cells. They are, however, only to be found on vessels down to 0.1 mm. in diameter besides on the capillaries of the oral mucous membrane of the frog. As far as the nerve-nets of *Remak* are concerned, *Leontowitsch* distinguishes between two types: "*A*" and "*B*", of which "*A*" corresponds with the classical description (*i. e.* a true nerve-net of nucleated, varicose fibres), while "*B*" differs, in so far as the nuclei are less numerous: "*Es kommt ein Kern auf eine grössere Anzahl von Nerven*".

To *F. B. Hoffmann* the question presents itself in a different light; he asserts that the innervation of smooth muscle is fundamentally identical everywhere: From a *fundamental plexus* branches pass to a *terminal plexus*, which is a true, peripheral "*Endnetz*". As to ganglion cells in the musculature — and especially the "ganglion cells" of *Bethe* — they are all a delusion; they are "*Kerne in der strukturlosen Nervenöhle*".

Similar results were arrived at by *R. Müller*, who found true nerve-nets in the gastro-intestinal canal of frogs — only intraepithelially did he see free nerve-terminations, and he also — like *Ramon y Cajal* in the same year — rejects the theory of *Bethe* of peripheral nerve-nets formed by short anastomoses between ganglion cells.

In 1908 *Michailow* examined the nerves of the endocardium, and in the blood-vessels he found one nerve-net in the adventitia and another in the muscularis. On the capillaries, on the other hand, he only saw one or two accompanying nerves, which observation caused *Botezat* to revise his observations of nerve-nets on the capillaries. In all the later works of *Michailow*, which were carried out by means of the methylene-blue method, he asserts that the nerve-nets are the ultimate terminations of the nerves in the vascular wall, even if he occasionally sees some few free terminations in his preparations — the fewer the more complete the staining is. Ganglion cells *Michailow* only finds outside the vessels, and only in certain organs (*heart*,

bladder). Also *sensory* nerve-endings were seen by *Michailow*; as to the *Vater-Pacini*-corpuscles there are few in the vascular wall itself and they are only to be found in the adventitia; on the other hand, he thinks that they are of the utmost importance to the blood pressure in the capillaries, and that in this way they may indirectly affect the blood pressure in the larger vessels. The investigations of *Michailow* in this respect were carried on by *v. Schumacher*, who in 1911 demonstrated that the *Vater-Pacini*-corpuscles swell when the blood pressure is raised artificially, while they are ordinarily found in a "collapsed" state; this might be due to the raised pressure in the intralamellar capillaries, and the corpuscles might in this way be able to influence the regulation of the blood pressure by means of a reflex.

Michailow himself dropped this question, but continued his investigations with work on the innervation of the heart in horse, dog, cat and rabbit. Only on the larger vessels in the myocardium did he find *medullated* nerves, which end in free arboroid terminations. On the contrary, *non-medullated* nerves are to be found down to quite small vessels — with the capillaries, however, *Michailow* thinks the nerves have no intimate connection. On the arteries a longitudinal plexus is to be found in the adventitia, and from this branches pass to a closer, transversely arranged "*Arteriengrenznervengeflecht*", which also receives branches directly from the perivascular nerves; from this plexus only a few branches pass into the muscularis which is mainly innervated from the adventitial plexus and directly from the perivascular nerves. "*Alle diese Aestchen und Fäserchen teilen sich, verflechten und verwickeln sich untereinander, wobei auch das Muskelgeflecht der Blutgefäße gebildet wird. Es lagert in den bindegewebigen Zwischenschichten zwischen den Muskelfasern. Mitunter gelingt es zu beobachten, wie vom beschriebenen Muskelgeflecht einzelne Fäserchen gehen, die mit knopfartigen Verdickungen an den Muskelzellen enden. Allein in solchen Fällen erwies sich das Muskelnervengeflecht selbst bedeutend lockerer und spärlicher; je dichter aber dieses Geflecht selbst in den Präparaten erscheinen, d. h. je vollere vollständige Färbung der Nervelemente mit Methylenblau man bekommt, desto kleiner erweist sich die Quantität dieser feinen, knopfartigen Endigungen auf den Muskelzellen der Gefäße und desto mehr und mehr verändert sich das beschriebene Geflecht in ein fest geschwollenes "Endnetz".*"

In the great "*Histologie du système nerveux*" (1911) *Ramon y Cajal* also finds plexiform nerves in the vessels and confirms the results of *Retzius*; like this investigator, *Cajal*, however, finds that the nerves in smooth muscle end in *free, bud-like, extracellular terminations*.

In 1913 and 1914 some papers by *Glaser* appeared; this worker, who began in collaboration with *L. R. Müller*, at first found no nerves in the muscularis of the blood-vessels, later on he stained the nerves by means of *rongalith-white* (see *Technic*) and now, in addition to a perivascular plexus, he saw a true anatomical net-work in the adventitia of the larger vessels,

veins as well as arteries; from this net branches passed to a nerve-net on the borderline between the adventitia and the media and in addition he saw, "*zwischen den Muskelbündeln ein feinmaschiges reich verzweigtes Netzwerk, das von sehr dünnen, mit Knöpfchen versehenen Nervenfäden gebildet wird*". These nerves ended in the muscularis in free, bud-like terminations. In the *intima* Glaser also saw nerves. The smaller vessels and the capillaries were provided with a longish plexus of nerves, or the vessel may be encompassed by a single nerve twined spirally round it. Some doubt, however, may be entertained of some of Glaser's results; firstly some of his nerves are strikingly similar to the elastic nets of the arterial wall — which are, moreover, stained almost specifically by the concentration of the dye ($\frac{1}{2}$ p. c.) which Glaser uses (see *Technic*); secondly his "*nerve-spiral round a capillary*" (reprinted later by several authors) is beyond a doubt — *not*, as Stöhr supposes, blood corpuscles — but rongalith-white-stained muscle cells on a little artery*).

In 1914 some dissections of the nerves to the arteries of the human arm by Kramer & Todd were published, and this work was carried on as to the inferior extremity by Potts. These workers find that the nerves of the arteries originate in the peripheral nerve-trunks, and that the innervation takes place *segmentally*, the result being that "*damage to a large artery will injure vascular plexus on point of damage only*". Even if these investigations are quite modern, they seem rather naïve. Of course it might be assumed that the dissected nerves were *sensory*, while the sympathetic, motor innervation took place *perivascularly*; these investigators have not reckoned with this possibility — nay, they do not even mention it. Other dissections from recent times have been executed by Hahn & Hunczek and by Hirsch, and they confirm the results of the Englishmen.

Hirsch, on the other hand, was not able to dissect nerves from the sympathetic trunk to vessels other than the most central parts of the *subclavian* and the *iliac* artery; on this basis he concludes that the innervation of the vessels of the extremities is *segmentally* arranged, and takes place along the peripheral nerve-trunks, but even this conclusion seems premature: Even if Hirsch was not able to dissect long nerve-trunks along the vessels, these nerves might very well exist as thin fibres or continuous plexuses in the inner parts of the vascular wall.

As a matter of fact other investigators really demonstrated by similar dissections (executed with Kondratjew's new method of impregnation for dissections) that continuous nerve-nets are to be found in the inner part of the arterial adventitia (Kondratjew, Ljetnik, Berglas).

That the previously disputed peripheral *microscopical* nerve-nets do

*) I have often myself seen the same picture in my preparations; the muscle cells frequently lie with a little interval between them and twined spirally round the vessel. The picture is very deceptive (an indication of what is meant may be seen in fig. 3).

E. B.

really exist, has been once more confirmed by E. Müller who, with the impregnation method of *Bielchowski*, found true nerve-nets in the stomach of sharks. On the contrary *O. Larsell* (1921) sees the motor nerves as well as the sensory nerves on the blood-vessels of the rabbit's lung terminate in free, bud-like endings, but *Larsell* admits that these endings originate in a nerve-net.

The most important modern investigations on the innervation of the blood-vessels are, however, of German origin; in 1921 *P. Stöhr jun.* examined the innervation of the human *plexus choriodei*, and continued the following years with investigations on peripheral innervation elsewhere (*renal capsule, bladder*). *Stöhr* works with a modification of *Schultze's* impregnation method (later on with *Bielchowski's* impregnation in the modification of *Valley Gross* (see *Technic*)), which, in his hands, gives remarkable results. On the *plexus choriodeus* and on the blood-vessels of the *pia mater*, *Stöhr* finds a coarse-meshed nerve-plexus in the outer part of the adventitia, and a closer, more irregular plexus in the part adjoining the media; he, however, finds no nerve-net in the muscularis, only "*vereinzelte Fasern von äusserster Feinheit*"; *Stöhr* did not, however, succeed in finding even these fibrils in the deeper parts of the media. On the veins a very irregular plexus is to be found. The sensory nerve-endings *Stöhr* describes almost as *Smirnow* and *Dogiel* did, and the capillaries, he finds, are accompanied by two or more nerves, "*die in feinen Aestchen mit knopfförmigen Anschwellungen auf der Gefässwand enden können. Nicht selten findet man Schlingelbildung von Fasern um die Capillaren*".

In his work on the nerves of the renal capsule, *Stöhr* again reviews the question and asserts: "*Capillarnerven müssen mit dem Endothel des Gefässes eine ganz innige Verbindung, meist unter Bildung von feinsten Endknöpfchen, eingehen, wenn sie mit Sicherheit als Gefässnerven angesprochen werden sollen*".

In his last work (1926) on the capillary nerves *Stöhr* changes his opinion, as he now seems to acknowledge the longitudinal nerve-nets around the capillaries as nerve-terminations, and he thinks that these must be capillary nerves *sensu strictiori*, because they, in some places, touch the capillary wall directly, and because, even if they leave the vessel, they only go to join other capillaries. In one place in one of his preparations *Stöhr* again sees the previously mentioned bud-like nerve-endings on the capillary wall.

Previous investigators' results as to nerves on the capillaries, *Stöhr* either seeks to explain away, or he mentions them cursorily as *artefacta*. Even on the nature of these nerves *Stöhr* expresses himself; while the previous investigators held the nerves of the capillaries to be sensory, there is now — after *Vimtrup's* demonstration of the *Rouget-cells* on the capillary wall — some cause to suppose that, besides possible sensory nerves, motor nerves

might also be found. Stöhr treats this problem in the following way: "*Langley sagt, meiner Ansicht nach mit Recht, dass kein wirklicher Beweiss für das Vorhandensein efferenter Sympathicusfasern zum Capillarsystem erbracht sei, da die einzige hierfür in Betracht kommende Arbeit von Steinach & Kahn, die Existenz von Rougetischen Zellen zu ihrer Contractionstheorie benötige, die aber bei den meisten Organismen gar nicht vorhanden seien. Krogh nimmt die Sache zunächst wesentlich einfacher und lässt auf Grund eigener Beobachtungen sowie der Arbeiten von Hooker, Steinach & Kahn, sogar jede einzelne Rouget-Zelle mit einem sympathischen Fasern versorgt und zur Contraction gebracht werden. Freilich nennt dies Krogh nur eine Annahme; dass sie aber ganz sicher unhaltbar ist, geht aus dem Fehlen der Rougetischen Zellen in vielen Fällen hervor, wie daraus, dass bis jetzt auch nicht ein einziger anatomischer Nervenbefund einen Anhaltspunkt für eine solche Hypothese liefern würde*".

Stöhr himself thinks that the nerves demonstrated are *not* motor nerves, but he supposes with Ohno and Odermatt that the dilatation and contraction of the capillaries is brought about by the influence of substances circulating in the blood, and that it is most probable that the function of the nerves of the capillaries is either secretory or sensory.

With regard to the ultimate relation between muscle and nerve, Stöhr, in his publication on the nerves of the bladder, accepts the intranuclear "*Endösen*" described by Boeke a. o. (Heringa, Dunn Garven, Laurentjew) — i. e. small ring-like structures which are supposed to end the course of the nerves ("*Feinste Nervenfasern, die von den zwischen den Muskelzellen befindlichen Endplexus abstammen, dringen in das Protoplasma der glatten Muskelzellen ein, um hier mit Oesenbildungen zu endigen*").*)

I shall therefore briefly mention the theory of innervation of smooth muscle which was brought forward by Boeke and his pupils; like Held, Boeke maintains the protoplasmic conduction-path, and in a later work Laurentjew thinks that Held's "*lemmoblasts*" may be identified with the *interstitial cells* described by Cajal, with Bethe's *net-forming ganglion cells*, and with the *sympathetic nerve-cells* of E. Müller. Besides the intranuclear "*Endösen*", Boeke finds a "*periterminal net-work*" in the protoplasm of the muscle-cell, which net-work trophically belongs to this cell, and which should be the morphological substratum for Langley's "*receptive substance*" (see *Physiol. Part*).

*) *Addition on proof-reading:* In his "*Mikroskopische Anatomie d. vegetativen Nervensystems*" (1928) Stöhr declares: "— in Hunderten von Präparaten habe ich nicht eine Spur von Nerven in der Muscularis bemerkt", and he sticks to his above-mentioned conception of the capillary nerves; however, he, too, has seen the *small "local" plexuses* of these nerves, and his description of these is in perfect accord with Ioris's and my own observations (p. 30 & 69 & fig. 22 a & b). E. B.

Much in this theory seems plausible, but a very large amount of work remains to be done before it may be considered reasonably grounded on facts.

To return to the morphology of the vascular innervation, *Glaser*, in his works in 1926—27, adheres to his previously mentioned conception of the innervation of the vessels, and it is clear that his opinions are represented in the large manual of *Müller: Die Lebensnerven*. *Glaser* asserts that, after plentiful anastomosing, the nerves end in bud-like, free terminations external to the individual muscle cell ("*Auch in der muscularis kommt es zu Endverzweigungen, die in kleinen Knötchen auslaufen*"). Concerning ganglion cells on the vessels *Müller* writes: "*Bedeutungswoll erscheint es, dass Ganglienzellen nur in der adventitia solcher Gefässe angetroffen werden, die in grossen Körperhöhlen oder in der Schädelhöhle verlaufen. — An den Gefässen der Extremitäten — konnte ich trotz fleissigen Suchens niemals Ganglienzellen feststellen*", and this observation covers the opinion of most modern workers; *Gehwolf*, however, in one case finds collections of ganglion cells in the vascular plexus of *vola manus*, but supposes this to be an anomaly.

In 1926 *Hirsch* proceeded with his work on the vascular innervation, this time with microscopical investigations (*Bielchowski's* impregnation in the modification of *Valley Gross*), but he did not by this means discover facts to support the supposition of long, perivascular nerves. In the adventitia *Hirsch* found medullated and non-medullated fibres, in the inner part mostly the latter; he cannot speak of any real plexus in the adventitia as he only sees longitudinal bundles with some few anastomoses. True nerve-nets *Hirsch* only found "*unmittelbar auf der Ringmuskulatur des Gefässes. In den tieferen Schichten gelang es mir nie irgend welche nervöse Elemente zu finden. Sämtliche Versuche weitgehendere Ergebnisse der Versorgung der Gefässmuskulatur zu erhalten, schlug fehl. Flachschnitte durch die muscularis der Arterien von Erwachsenen, Anwendung anderer Silbermethoden, supravitale Färbung von Kalbsarterien mit Methylenblau und Rongalithweiss, der Erfolg aller dieser Versuche war völlig negativ*". *Hirsch*, moreover, maintains that as yet we have not one single satisfactory proof that nerves really are to be found in the *tunica muscularis* of the blood vessels, and — with some justice — he criticises the drawings of *Dogiel* and *Glaser*. In addition he declares that of the ultimate relation between muscle and nerve nothing definite is known as yet: "*Vielleicht fehlt überhaupt den letzten Enden der Nerven-fibrillen, die Fähigkeit Silber zu reducieren bzw. Farbstoffe vital zu speichern. Vielleicht ist auch keine direkte Beziehung der Nerven mit der glatten Muskelzelle zur Funktion notwendig*".

Against the "free, bud-like nerve-endings" of various investigators, *Hirsch* cites *Hoffmann's*, *Bethe's*, *Dogiel's* and *Michailow's* observations that the more complete the staining, the fewer are the "free nerve-endings" to be found.

Hirsch has often seen the capillaries accompanied by nerves, which sometimes run parallel to them, sometimes twine round them. Finally *Hirsch* gives some very beautiful drawings of *Vater-Pacini*-corpuscles in the adventitia of various vessels.

Also *Fukutake* (1925) doubts the intranuclear "Endösen", which he ascribes to incomplete staining, and he continues: "*Sowie Hoffmann und Michailow sehen wir die feinsten noch verfolgbaren Fäserchen den Muskelfasern dicht anliegen, ohne aber ein eigentliches typisches Endgebild zu zeigen. Man muss also ausgedehnte Strecken der Verzweigungen als Endfasern annehmen. Man kann sich oftmals des Eindruckes nicht verwehren, dass alle diese feinsten Fasern so innig mit der Muskulatur verbunden sind, dass eine Uebertragung irgendeiner Wirkung, etwa auch im Endteil ihres Verlaufes, nicht nur an den Punkten der eigentlichen Nervenendigung denkbar wäre, besonders da sich diese letztere morfolologisch kaum von den vorübergehenden Strecken unterscheidet*".

Laubmann, Kadanoff and *Dowgjallo* likewise find nerve-nets in the vascular wall, without, however, entering into detail about the ultimate nerve-endings.

Woollard — who in 1926 finds intracellular nerve-terminations in the myocardium — is not able to find such in the smooth muscle of the wall of the blood-vessels in the same year, and he thinks that there is a fundamental difference here between smooth and striped muscle. In the vascular walls of various animals *Woollard* finds a close net-work in the muscularis: "*The innervation of the muscular coat by this fine net-work, the individual elements of which divide and fuse so as to give absolute continuity, is complete throughout the vascular tree*". From this net-work small, very short branches originate, which end extracellularly in a little swelling. *Woollard* finds sensory nerves, too, in the vascular wall; these may end in a *Vater-Pacini*-corpuscle, but mostly they end in free bud-like terminations in the adventitia, while they are not to be found in the muscularis.

The result of this chapter may be summarised as follows: The old contest as to free nerve-endings or terminal nerve-nets is still going on. While a few investigators think that *the muscularis of the blood-vessels perhaps does not contain any nerves at all*, others are of opinion that innervation takes place through *peripheral nerve-nets*, which may either be quite closed and extracellular or may give off branches which end in *free terminations external* to the muscle-cell; and still other workers assert definitely that every single smooth muscle-cell has an *intracellular, intranuclear nerve-ending*.

Nor can any agreement be said to exist on the question of the relations between the sensory and the motor nerves to the vessels — whether they

form joint nerve-nets or whether they run independently of each other in the vascular wall.

As some surgeons, moreover, surmise that peripheral nerve-centres with trophic influence exist, the temptation to take up these questions for serious consideration is great; when once the interest is awakened by working at these problems, a great field for investigation opens out.

Even if one cannot hope definitely to clear up these problems, at which so many and such prominent workers have laboured, it would seem a sufficiently great thing to contribute even ever so unpretentious a share to the elucidation of these fundamental questions.

TECHNIC

*Dans l'investigation scientifique les moindres
procédés sont de la plus haute importance.*

Claude Bernard.

FOR investigations like these it would be of the greatest importance to possess a method of nerve-staining, by which even moderately constant results might be obtained, and by which the histological elements which are the object of study would be safely stained.

The existing methods of nerve-staining in peripheral tissues may be divided into two fundamentally different groups: Methods of *impregnation* and methods of *vital staining*. While the various impregnations give rather constant results, this cannot be said of the methods of vital staining. On the other hand, the last-mentioned proceeding sometimes seems to yield more than the impregnations, in so far as nervous elements which either are not impregnated at all or only badly impregnated, may sometimes be stained vitally. Consequently the results obtained by the two different modes of procedure do not quite correspond, and the constant disagreement between the partisans of the two different *modi operandi* may in no small part be due to this circumstance.

While very beautiful results were obtained about the middle of the last century by very primitive methods (simple preparation, acetic acid, later *Loewit's* chloride of gold and *Golgi's* silver method), this has not been the case with modern workers, who perhaps demand methods involving less personal labour than the previous investigators were prepared to give. At any rate the results of *Beale* (1860—1870) and *Krimke* (1880), only to mention a few, seem quite equal to the best modern investigations. Very often, however, the earlier communications have a rather fragmentary character — perhaps just because the technic took so much of the time available for the investigations: One successful preparation was something on which to base a theory. It was therefore a great advance when the epoch-making vital staining with *methylene-blue* was introduced by *Ehrlich* in 1885; but even this method had its drawbacks. It is significant that really good results have only been attained by a few investigators (especially *Dogiel* and his pupils, *Leontowitsch*, *Retzius* a. o.), while other workers were only in a very small degree able to reproduce the discoveries of these masters; this is without doubt due to the fact that even this method demands great personal skill — a skill which is frequently only attained by considerable practice. And this is especially true if constancy in the staining of a series of preparations is required, so that the same elements are again and again stained under the same conditions. But this, especially, is the weak point of vital staining: Due

to the many different factors, (oxygen tension, acidity etc.) — in brief to the condition of the tissue at the moment of staining — factors, which cannot as yet be controlled and which are barely known, the staining will again and again give the most different results. Even if many relations are elucidated by the work of previous investigators since *Ehrlich* published his discovery in 1885, it still remains to improve the technic in such a way that it will give really constant staining, by which alone a continuous series of investigations is possible.

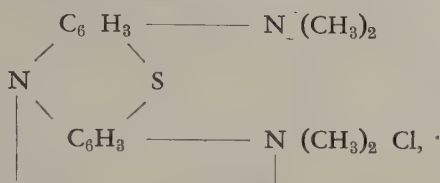
For these reasons I was at first most inclined to employ one of the various methods of impregnation in the present work. However, preliminary experiments in vital staining yielded such beautiful results that, in spite of the aforementioned shortcomings, I decided to employ this method. It was a concurrent motive that various impregnations had recently been employed by prominent histologists (*Stöhr jun.*, *Hirsch*) in the very field singled out for study in this work, without yielding essentially new facts — nay even without being able to bear out the discoveries of previous workers. Moreover, "vital" staining seemed *a priori* to afford a better chance of studying the nerves in as "natural" a state as possible. Of the various methods only *Ehrlich's methylene-blue method*, which *Retzius* names "*eine der bedeutungsvollsten Errungenschaften der neuesten histologischen Technik, wenn nicht geradezu die vornehmste derselben*", seems to have been of any importance for neuro-histology, and, influenced by these reasons, I decided to adopt this method in my work — all the more so because after a time I succeeded in working out a technic which — in my hands at any rate — gave substantially more constant results than the previously used modifications.

Vital Staining by Ehrlich's Methylene Blue.

As mentioned above methylene-blue was first used for the purpose of staining nerves by *Ehrlich*, who described his discovery in a lecture on December 21, 1885 in *Verein für innere Medizin in Berlin*. He simply injected a concentrated solution of the dye in the vessels of frogs and after this he found the nerves in certain localities, especially the tongue and the palate, stained a deep blue, the surrounding tissue being all but colourless. *Ehrlich* describes his discoveries in a later communication, but evidently it has been of no interest to him to use the method for a thorough study of the morphology of the nerves. However, in 1890 he mentions the possibility of utilising therapeutically the avidity of the nervous tissue for methylene-blue. As is well-known, however, this idea led to nothing.

In addition to methylene-blue *Ehrlich* discovered several related substances, through which it was possible to obtain a partly elective staining of the nerves; these substances, however, have been of no importance and will not be mentioned here.

Methylene-blue (*tetramethylthionine-chloride*) has the formula



and is generally employed in this form. In addition *Kreibich* (1913) recommended *rongalith-white*, introduced by *Unna & Golodetz* in 1910—*i. e.* methylene-blue to which is added a reducing base, *rongalith* (SO_2Na) on the supposition that the staining would be more intense when the leuco-product (*methylene-white*) was transformed to methylene-blue at the moment of staining—the base is liberated in contact with organic tissue. In the present work both substances have been used, without any essential difference being noted in the results. Staining by *rongalith-white* seems, however, to be less specific, the result being that a more dilute solution must be used—giving in so far a stronger action.

The substances are applied in solution—generally in an isotonic solution, most frequently *NaCl*, sometimes *Ringer's* or *Locke's* solution. The various investigators have used very different concentrations, and I have not succeeded in finding any agreement between them. This may partly be ascribed to the investigators not having allowed for the difference between warm-blooded and cold-blooded animals; while the frog may be subjected to nearly saturated solutions without the staining being particularly unspecific (when the process does not take too long), the tissues of warm-blooded animals are far more sensitive. By varying the conditions (of concentration and time of staining) I have succeeded in getting elective staining by methylene-blue of *nerves*, *smooth muscle*, *connective tissue* and *elastic tissue* separately. For the staining of nerves *Woollard* uses .02 p. c. methylene-blue in isotonic solution of chloride of sodium. In my opinion this is too high a concentration for staining by injection in warm-blooded animals. My best results were obtained with 0.01 p. c. methylene-blue, dissolved in the same manner; of *rongalith-white* still less should be applied—about 0.005 p. c. For supravital staining on slides still weaker solutions should be used—about half of the concentration used for injection. Very often, however, one is disappointed by the different reaction to the same concentration of dye by different animals even of the same species—this was especially inconvenient before the introduction of the modification used in the latter part of this work.

How should the dye be applied? *Ehrlich* exclusively used the dye by injection into the living animal. Some years afterwards it was noted that the

staining was successful even in animals just after death; often, however, this proceeding only yielded incomplete staining, and several workers therefore endeavoured to find out the factors which determined the different results of the staining. *Aronsson* (one of *Ehrlich's* pupils) was among the first to stress the importance of the *oxygen*; in his first communication *Ehrlich* himself mentioned this as a possibility. *Ehrlich's* theory of the staining as a really "*vital*" process was attacked by *Frey*, who asserted that on the contrary the nerves were only stained at death, and that the staining was then brought about by the oxygen of the air. Moreover, it was noted that the staining in animals killed by suffocation was often incomplete, but that the staining sometimes appeared when the tissue was for some time spread out in thin layers on a slide. *Dogiel* sought to utilise this discovery, introducing *supravital staining on slides*, by which he thought he could obtain more constant results. Later investigators have divided themselves between this method and the staining by injection in living or freshly killed animals, and the difference between the results of the two methods does not seem of any great significance to me; frequently both methods fail, without it being possible to show any alteration even in a single particular in the usual technic.

In 1906, however, *Leontowitsch* began to subject tissue removed after injection-staining of amputated human extremities to an "*after-staining*" in a moist chamber with oxygen (a small bell-glass filled with oxygen placed on a glass plate*). For while oxygenation by the oxygen of the air often proceeds so slowly that a real oxygenation is not attained until the tissue is dead and all specific staining thereby excluded, with this technic he thought he could obtain a greater percentage of good staining than previously. This method, too, I have tried, but it is also very capricious; the staining especially suffers very much through the necessity of removing the tissue from the moist chamber for microscopic control, after which the chamber must once more be filled with oxygen etc., and moreover the aëriform oxygen as a rule only stains the surface of the tissue, which may remain quite unstained in the deeper part. Finally the method was not suitable in this work, where in consequence of the nature of the material (from surgical operations) I could not as a rule at once proceed to the staining.

Even if supravital staining thus did not make good all it promised, nevertheless, in my experience, it was the safer method, and for an essential part of my material (from humans) the only one possible; and by some

*) According to oral communication of Professor, Dr. med. F. C. C. Hansen of the University of Copenhagen, oxygen was used for "after-staining" of methylene-blue-stained crustaceans as early as the nineties at the *Institute of Normal Anatomy in the University of Copenhagen*.
E. B.

small modifications I finally succeeded in obtaining a technic which proved satisfactory for my purpose.

Fixation. In addition to the drawbacks mentioned above, staining with methylene-blue has the defect of not being durable. Without fixation, the colouring is only specific for about 10—60 minutes, the time varying widely with the condition of the tissue. In 1887 *Smirnow* discovered that *Hoyer's picrocarmine* seemed to have a fixing influence on the stain. Previous to this *Smirnow* (a pupil of *Arnstein's*) had obtained a slight fixing effect with *iodine*, but this had had no practical importance. A short time afterwards *Dogiel* found that the fixing substance in the picrocarmine was *the picrate*, consequently he introduced fixation with an aqueous solution of picrate of ammonia. But even this fixation had its defects; it turned out that the fixation was not durable, and so as not to be decolorised, the tissue had to be preserved in solutions saturated with picrate of ammonia; and consequently these preparations could not be dehydrated.

Dogiel therefore preserved his preparations and simultaneously rendered them transparent in a mixture of picrate of ammonia, water and glycerine. Even then the preparations lost in colour, but in this way they might sometimes be preserved for as long as half a year.

Later on several different methods of fixation were proposed. Of these *molybdate of ammonia*, introduced by *Bethe* in 1895, has been of the greatest importance. *Bethe* employed it in a 5—10 p. c. aqueous solution with the addition of H_2O_2 to prevent the staining from fading for want of oxygen; the fixation was carried out at 0^0 , as it then seemed more stable (this, however, is denied by *Dogiel*). Though I have tried the various different formulas of *Bethe*, each for its definite purpose, nothing can — in my hands — compete with the picrate of ammonia of *Dogiel*, which *Vimtrup*, too, found the best mode of fixing methylene-blue staining. In picrate the fixing is nearly instantaneous, while the staining is often carried on for some time in molybdate, which damages the preparations very much; nor does a combination of the two proceedings (*Leontowitsch*) give better results than picrate alone (*see* p. 49). Even if paraffin sections cannot be made with this proceeding (because owing to the lability of the fixation the preparations cannot be dehydrated), beautiful sections may be obtained with the *freezing-microtome*, the sections being made in the picrate-solution before they go into the glycerine-mixture for clearing. A graver drawback is the maceration of the tissue which takes place in the picrate-solution, but in the present work this has been rather an advantage, as the thick arterial walls are made more transparent.

I shall now proceed to a close description of

The Technic Followed in the Present Work.

In preparatory experiments all the previously known modifications were tried without any really satisfactory result. Even when I sometimes

got beautiful pictures, the staining was quite capricious, the consequence being that nothing could be concluded from negative results. This being a *conditio sine qua non* for employing the method in degeneration-experiments, these methods could not be used.

During the first experiments it was, moreover, evident that the staining, especially with *rongalith-white*, carried out according to the previously communicated directions, was very unspecific — as I found out later because I stained with too strong concentrations and for too long a time. A definite relation — but varying with the condition of the tissue — seems to exist between the *concentration* used and the *time* which the dye takes to act. But in spite of the greatest care, all the methods which were tried might suddenly fail without it being possible to ascertain the cause.

On experimenting with the different methods *supravital staining a. m. Dogiel* seemed to give the most constant results, but, on the other hand, the staining was less complete than after injection of the dye. To obtain complete staining two factors seem of vital importance:

1. *The tissue must within a certain time (i. e. probably before its death) be saturated with the dye.*
2. *The tissue must be saturated with oxygen, without which the absorbed dye does not turn blue, but remains in the tissue as a leuco-compound — and this, also, must happen before the tissue is dead, after which the staining becomes unspecific.*

To fulfil the first condition I determined — like *Krebs* in 1905 — to stain by diminished air-pressure, by which proceeding the dye was supposed to be better able to penetrate into the tissue, the interstices bursting open when the absorbed air was drawn out. To fulfil the second condition H_2O_2 was obviously quite unfit — the tissue was deeply affected by the strong, but quite superficial oxygenation and the colouring faded.

After some experimenting I arrived at the following technic:

Immediately after its removal from the living or freshly killed organism the tissue, in which nerves are to be stained, is dropped into a solution of methylene-blue (*Grübler rectificatum, nach Ehrlich zur Injektion*) 0.01 p. c. in isotonic, body-warm saline solution or in a similar solution of *Rongalithweiss* (*Grübler*) 0.005 p. c. The tissue lies in an ordinary *Dreschel's* washing-bottle and the volume of the solution should be 10—20 times greater than that of the tissue. The rubber tubing on the long tube is closed with a clamp, and through the short tube the bottle is rapidly sucked free of air by the water-suction-pump. During the first minutes numerous bubbles are seen to break upon the surface, and a short time afterwards the solution "boils" under the diminished pressure. When the solution has "boiled" for a few minutes, the short tube of the bottle is closed by a clamp, the connection with the pump is broken off, and the bottle is placed in the incubator (37°) for about

fifteen minutes. It is then taken out, and the tubes are opened (simultaneously). The long tube is then connected with an oxygen-container and a brisk stream of oxygen is conducted through the bottle. After 5—6 *minutes* the short tube is first closed, then (when the stream of oxygen is slowing down owing to the increasing pressure), the long tube, too, and the bottle is again placed in the incubator. After a certain time (varying for the different animals, *see below*), the bottle is taken out, the tubes opened (simultaneously), the fluid is poured off, and the bottle is filled with a saturated aqueous solution of *picrate of ammonia*. The tissue is fixed in this bottle for 6—24 *hours* (varying according to the thickness of the tissue), and is then transferred to a bottle with an abundant amount of the following mixture:

saturated aqueous solution of picrate of ammonia

glycerine (ordinary) $\bar{a}$ partes (to be shaken thoroughly),

in which it passes 6—48 *hours* (thick pieces (*i. e.* thicker than 2—3 mm.) preferably 3—5 days). The tissue is then taken out, spread out in the manner most practical for examination, squeezed between two slides (thick pieces for some hours by means of two small clips) and placed under a cover-glass in the glycerine-mixture mentioned above. The cover-glass is edged round with black enamel paint (quick-drying) or with wax.

Remarks.

1. If the preparations originate from animals it is better to combine the above proceeding with the *injection of dye*, especially if the finer nerves of the vascular wall are to be stained. The injection may be *intravascular* or by *infiltration* of the tissue.

In *intravascular injection* the vascular system should be thoroughly washed through with an isotonic, body-warm saline solution, or else the blood corpuscles will absorb most of the dye and too little will remain for the surrounding tissue. The injected fluid should be abundant — about the blood-volume of the animal (or the blood-volume which is judged to be contained in the part of the body in question). It is best not to inject with a syringe (spasms in the arteries!) but under constant pressure — *e. g.* through a funnel connected with the canula by means of rubber-tubing. In the funnel, which should not be too large (to prevent cooling!), is poured the saline solution, and subsequently the dye — for warm-blooded animals 0.01 p. c. A certain time is necessary before the dye diffuses into the tissue; most workers therefore recommend waiting for a certain time before excising fragments for examination. It is, however, very difficult to determine this time, since it varies with the differing condition of the tissue. Because of this *Hosch* terms this "*das allerheikelste Punkt der ganzen Arbeit*": If the time is too long, the stain has faded, if it is too short, the dye will not have penetrated sufficiently into the tissue. These difficulties may be avoided by

using the modification described above: The tissue is excised any time during the first half hour after the injection and is then treated as usual.

In *staining by infiltration* of the tissue the dye is injected into the vessels and their surroundings, thereby being subjected to a certain pressure; the tissue is then excised and treated as above; this method combined with intracardial injection gives particularly good results in the web of the frog, in which — for some unknown reason — it is very difficult to obtain a good staining of the nerves. The dye is injected at the base of an interstice, whereupon the two layers of the web are easily separated and can be removed for examination.

2. *Staining with rongalith-white*. As mentioned above, this compound seems to stain stronger and less specifically than methylene-blue. Yet — with the necessary practice — it gives just as beautiful pictures, and in the end I used the two substances indiscriminately. This compound, however, has no advantage over methylene-blue and consequently it seems rather superfluous. It is employed for this purpose in about half of the strength necessary for methylene-blue — in warm-blooded animals in a concentration of 0.005 p. c., dissolved in the same way. It is supplied from *Grübler* in brown bottles and is quickly spoiled when the stopper does not fit.

3. *Supravital staining a. m. Dogiel*. This method is the easiest one for cold-blooded animals and, *e. g.* for the sensory nerves in the frog's skin, gives most excellent results. It does not, however, present any definite advantage except its simplicity and is almost useless in warm-blooded animals; but even in these it is possible to obtain an incomplete nerve-staining by letting the tissue (very small pieces) float on a water-bath (ca. 40°) in a watch-glass with a 0.005—0.01 p. c. methylene-blue solution. As will be mentioned later, this method is very helpful in the study of the innervation of the *Rouget-cells*. The staining is controlled microscopically — when it seems optimal, the preparations are fixed.

4. *For how long is it necessary to treat the preparations with oxygen?* In cold-blooded animals a few minutes will suffice — when the bottle is filled with oxygen, it stands for some minutes at the usual room-temperature, and thereupon the tissue is fixed. In warm-blooded animals the time varies but little, mostly according to the thickness and compactness of the tissue, — from a quarter of an hour to half an hour. With thick preparations from human vessels it may be advantageous to let the tissue remain somewhat longer — but not over three quarters of an hour. Usually a quarter of an hour will be found suitable for vessels which have been cut open, thin muscles, bladder etc. (*i. e.* tissue of a thickness of up to 2 mm.), but the determination of the correct time *must* be a matter of practice. If the tissue is subjected to oxygen for $\frac{1}{4}$ — $\frac{1}{2}$ hour some nerves at any rate are sure to be stained.

5. *Picrate of ammonia*. Of the two modifications, the *yellow* and the *orange*, the last-mentioned is absolutely to be preferred. Numerous preparations were lost to me before I realised that the yellow was by no means equal to the orange compound in fixing the stain. The best procedure is to add picrate of ammonia in excess to the water, and filter the solution before use. It is *not* necessary — as in using the fixatives recommended by *Bethe* — to cool down to 00.

6. If it is a matter of great importance to get *paraffin sections*, the best proceeding is the one described by *Leontowitsch*: First, for one half to one hour the tissue is fixed in picrate of ammonia and subsequently for 4—6 hours in an 8 p. c. solution of molybdate of ammonia; thereupon the tissue is dehydrated as quickly as possible (*at once* in absolute alcohol) and embedded in paraffin, but the staining always suffers somewhat.

7. After fixation the preparations may *be cut with the freezing-microtome*. The sections then go into picrate-glycerine (see above) and are mounted like the other preparations.

8. *The durability of the preparations*. As to this nothing definite can be said. Several of my preparations are as good as ever one year (*later two years*) after the preparation, while other preparations seemingly treated in quite the same way are very much faded. Especially the staining of sensory nerve-endings seems unstable — it often fades one month after the preparation, while that of the sympathetic fibres keeps better. It is of no importance whatever, wheter the preparation is quite surrounded by enamel paint or wax — several preparations which were not treated in this way at all were quite unchanged half a year later.

What Can Be Seen in the Preparations Stained in this Way?

The predominating colour of the preparations is the yellow of the picrate; the methylene-blue-stained elements are seen in all possible shades from black-violet to mauve and red, giving a very distinct contrast, even though they are not as distinct as in the fresh, unfixed preparations.

In preliminary experiments I often, in one preparation, saw *e. g.* the medullated nerves stained, while the non-medullated nerves and the nerve-endings were nowhere to be seen; in another preparation the reverse might be the case. The reason is that the various elements are stained at different times when the staining takes place exclusively by the oxygen of the air or of the tissue: First the non-medullated nerves and the nerve-endings are stained, some time after this the medullated nerves, but by this time the elements first stained have as often as not lost their colour. After having

introduced the oxygen-method mentioned above, I as a rule succeeded in staining all the elements in the same preparations — and the cause of the difference in the time of staining is consequently to be found in the oxygen-tension or factors parallel with this, factors which, at any rate partly, are eliminated by the aforementioned procedure.

Besides nerves the *nuclei of the smooth muscle-cells* are stained by the technic described. This is very advantageous for the question of the localization of the nerves in the vascular wall, allowing a sure determination of the plane in which the nerves are lying. The protoplasm of the muscle-cell itself is not, or only faintly, stained — except when the staining is carried on for too long a time (over $\frac{3}{4}$ hour), but then the staining of the nerves is nearly quite faded, except in the larger medullated trunks.

The *Rouget-cells* described at length by *Vimtrup* in 1922 behave like other muscle-cells of the vessels; as it is impossible to recognise these cells by the nuclei alone, I had to use a special method to get an impression of the relations of the nerves to these interesting cells (*see* p. 68).

Elastic fibres and connective tissue are not stained when the technic described is used. On the other hand, a very beautiful staining of the elastic nets may be obtained by using concentrated solutions ($\frac{1}{2}$ —1 p. c.) with subsequent fixation in the molybdate of ammonia of *Bethe*. That I have stained nerves in a given case and not other fibrillated structures, I have ascertained in every case by following the doubtful fibres back to unquestionable nerve, and for this reason I have almost exclusively studied *whole* preparations ("*Quetsch-präparaten*") in the present work and not sections, in which such a procedure is often impossible. Moreover, I have ascertained that nowhere in the preparations were unquestionable elastic or collagene fibres stained; finally with some practice it is *in some few cases* possible to determine if a certain stained fibre is or is not a nerve, but in this respect it is advisable to be very cautious and not rely thereupon.

Cell-limitations. That the nerve-nets of the vessels later to be described are not delusions produced by staining of the limits of the endothelial cells, is easy to demonstrate for the larger arteries. If these are cut open and examined with the intima towards the observer, no nets are seen. For the smaller and quite small vessels the demonstration is usually just as easy. Most frequently the nuclei of the endothelial cells are not stained, and this would most certainly be the case if the aforementioned structures were cell-limitations and methylene-blue has been used. Moreover, the arrangement of the nerve-nets often quite obviously makes it impossible that they could be cell-limitations. Finally, every single fibre is most frequently seen distinctly round and fibrillary, presenting a most typical appearance (*fig. 2*).

Whether or not a nerve is medullated is usually easily determined. The axis cylinder is stained deeply violet to mauve, and is surrounded by the medullary sheath as a diffusely stained reddish sheath; the *nodes of Ranvier*

are quite black — at least just as distinct as after impregnation. If, however, the methylene-blue staining is incomplete, or if the staining is carried on for too long a time, it may be difficult, sometimes impossible, to settle the question.

The non-medullated nerves are also distinctly stained, as a rule mauve or violet coloured. For the demonstration of these nerves especially methylene-blue staining seems superior to all other methods. It is of course unpractical to study the quite thin fibrils in the thick "*Quetsch-präparaten*", but as mentioned above, I did not deem it safe to employ sections; however, I at last succeeded in obtaining preparations which could not only be studied in all details, but from which it was even possible to get micrograms.

The nuclei of Remak are plainly seen, usually of a reddish colour.

Ganglion cells are also stained beautifully with the technic employed. The nucleus is definitely to be recognised, vesicular; these cells especially show beautifully in the plexus of *Auerbach* in the intestine of the animals employed. The impregnations, however, seem to be superior in this field when distinctness is required.

Sensory end-corpuscles are likewise better demonstrated by impregnation; by staining with methylene-blue the structure is not seen in details; it was, however, usually possible to recognise these structures — especially in slightly over-stained preparations or when the preparations were examined as the staining proceeded. The extracapsular course of the nerves to the end-corpuscles is, however, clearly to be seen.

As a whole the technic employed seemed well adapted to the problems of the present work. The staining of nerves with methylene-blue, however, is, in spite of all, a very exacting method; it cannot but be that much personal work will always be required when this nerve-staining is to be applied in peripheral tissue, but this is certainly no less true of the impregnation methods.

I have found the technic described equally useful in all the animals employed; in *frogs, mice, guinea-pigs, rabbits* and in *man*; the oxygen-method is especially very helpful in human preparations. As is only natural, it is often impossible to proceed at once to the staining of the excised tissue, and my first failures in staining nerves in human vessels may safely be ascribed to the fact that the tissue was saturated too late with dye and oxygen; by the quicker staining and oxygenation as described above it is possible to be in time, and it is possible to get good results even in tissue excised several hours before staining.

For a few supplementary investigations various *impregnations* were employed — especially at the start — none of them with very good results. Even if well-coloured nerves were to be seen elsewhere in the preparations,

I never succeeded — any more than *Hirsch* and *Stöhr jun.* — in impregnating nerves in the muscularis of the vessels. These methods, on the other hand, may be successfully used in the staining of nerves in the adventitious coat, but even here it seems as if the finer non-medullated fibres are not impregnated — nor is it altogether improbable that these fibres lose their power of impregnation during preparation, whereas they very well may be stained vitally. The method giving the best results in my hands was the well-known *Bielchowski* impregnation in the modification of *Valley Gross*, which method was also used by *Stöhr jun.*, *Hirsch* and *Lawrentjew*.

THE AUTHOR'S OWN INVESTIGATIONS

FROG

(RANA ESCULENTA & TEMPORARIA)

Notes: In cold-blooded animals it seems of less importance *how* the dye is applied — nerves are nearly always stained. Frequently it is sufficient to inject a few ccm. of a 1 p. c. solution of the dye into the lymph sack of the frog; after a few minutes the mucous membranes to which the air has free access, are seen to be faintly blue; if *e. g.* the mucous membrane of the palate is excised at this moment, the nerves will be seen beautifully stained. If simultaneous staining of the medullated and non-medullated nerves is required, it is best, however, to employ the usual method of staining in oxygen. Finally, if the *vascular nerves* are to be specially studied, it is best to inject a 0.01 p. c. solution of methylene-blue through a canula into the aorta, and the staining can then be continued with excised pieces placed on slides; while the staining is in progress the tissues are examined between two slides, one of which is removed between the examinations to give the air free access — or the tissue may be treated with oxygen as usual.

The small dimensions of the frog provide good conditions for studying the innervation of large vessels such as the aorta, as this vessel with its surroundings (*trunci sympathici*) may be examined as a whole in *one* preparation. The innervation of these vessels will therefore be especially treated in the description of the vascular innervation of the frog.

Aorta. Even before the staining is still quite complete, thick bundles are seen to proceed from the two sympathetic trunks to the aorta, there making mutual connections and forming a coarse-meshed plexus, in which — especially in the places where the *aa. mesaraicae & renales* issue — large collections of *ganglion cells*, readily recognised by the characteristic yellow pigment, are to be seen. As the staining proceeds, these bundles are recognised as large bundles of nerves consisting mainly of non-medullated fibres, intermixed with a few medullated nerves. The aforementioned plexus in the adventitia is formed by the greater bundles (often 0.05—0.1 mm. thick) dividing into two or three nearly equal branches, and these may again make connections with similar bundles; a true anatomical net-work (*rete*) is, however, nowhere to be seen, but only a coarse-meshed and rather varying *plexus*. Besides these large connections, one single, thick, non-medullated nerve, provided with large nuclei of *Remak*, is frequently seen to detach itself from a bundle and this nerve after a rather straight course, again joins another bundle of nerves. Anastomosing takes place between nerves from the same as well as from the two different sympathetic trunks. As already

stated by Jegorow, the left trunk gives off considerably more branches along the mesenteric artery than the right, while, on the other hand, this trunk chiefly innervates the distal part of the aorta. — The aforementioned ganglion cells are well stained; the nucleus is definitely vesicular, while the nucleolus, on the other hand, is not so distinct as with impregnation *a. m. Bielchowski*. Several of the single, non-medullated nerves mentioned above go to the cells, but in the thick preparations I have never been able to observe how they end, and have not stressed the point. The axis cylinders of the cells, however, might often be followed for a considerable distance, after which they were lost in one or other of the nerve-trunks.

If the aorta is dissected out, cut open, and squeezed between two slides the nerves which penetrate to the deeper parts of the vascular wall may be followed. It is thus possible to follow nerves, most frequently bundles of non-medullated fibres which, from the adventitial plexus, pass obliquely into the deeper parts, most frequently running transversely to the axis of the vessel. After a short course through the adventitia, in which they do not divide or anastomose with other fibres, these nerves suddenly divide and immediately upon the media they form a true anatomical net-work (*rete*) with predominantly rhomboidal meshes; at the points of division a nucleus of *Remak* is invariably to be seen. The size and form of the meshes may vary to a certain extent (according to the state of contraction of the vessel) and the meshes may sometimes be longish, narrow, sometimes almost square. The nerves are of about the same thickness as the afferent nerves to the net ($2-3\ \mu$) and are of a distinctly fibrillar appearance. The general course of the net is, however, always along the axis of the vessel — never athwart. This nerve-net entirely surrounds the aorta and forms as it were a closed net-work.

In good preparations it is possible from this net-work (*rete interlamellare*) to follow fine, non-medullated nerves still deeper; these fibres frequently issue from the points of division of the interlamellar net, but they may — though seldom — be seen to originate from the part of the fibres between two nuclei of *Remak*. While the nerves of the interlamellar net are of a distinctly fibrillar appearance, these last nerves are in part thinner ($1\frac{1}{2}-1\ \mu$), and in part they are not plainly fibrillar, but present a granular "varicose" appearance. The granules are a vivid blue and lie in rows within a paler-stained, peculiarly mucous, protoplasmic-like substance. These fibres, shortly after having penetrated into the muscularis, divide and form a nerve-net, which penetrates through all parts of the muscularis, the fibres entwining the individual nuclei of the muscle-cells, which are strongly stained. This net not only extends in *one* plane — as is the case with the interlamellar net — but continues throughout the whole thickness of the media, every single fibre dividing into 3—4 other fibres, all of the same thickness and appearance, of which branches two, *e. g.*,

continue in the same plane and here form a new mesh, while two or more go deeper, and after a short course which corresponds fairly regularly to the general length of the other meshes in the net, divide into two or more branches each of which forms new meshes. The average length of the side of a mesh in the net is about 20—30 μ and the course of the meshes in this *rete musculare* is chiefly transverse to the axis of the vessels — contrary to the course of the meshes in *rete interlamellare*; this arrangement is fairly constant, while, on the other hand, the length and appearance of the meshes vary to some extent.

Though this net-formation is continued through the whole of the muscularis, a definite difference in the *dimensions of the meshes* may be noted in the external and the more internal parts of this coat, the dimensions gradually increasing inwards, while the single fibres do not particularly decrease in thickness. This is most plainly to be seen in preparations examined with the intima upwards in comparison with other preparations of the same aorta. The dimensions of the meshes from the inner parts of the aortal wall may be up to double the dimensions of the meshes in the outer parts of the muscularis, but always they keep their arrangement transverse to the axis of the vessel; the fibres are judged to be about the same thickness as in the outer layers and the same "granular-mucous" appearance is retained.

In the *intima* itself I have never seen nerves — on the contrary the nerves of the inner parts of the muscularis can only be seen distinctly when the endothelial cells are removed (by a little fine brush).

Free nerve-terminations I have never seen in the media of the aorta — where for a moment there seems to be a bud-like ending, a slight turn of the micrometer-screw shows the fibre continuing in another plane. The *rete musculare* is completely closed everywhere, and nowhere (with complete staining) is one free nerve-ending to be seen.

In the preceding description a single bundle of nerves has been followed in its course inwards in order to give the best picture of the conditions. These, however, are not always so easy to unravel, because, besides the nerves just described, *other nerves* are to be seen on the aorta. In addition to the aforementioned nerves, which may for the present be named *the reticular nerves*, others are seen — though comparatively few in the frog it is true — which from their appearance alone can only with difficulty be distinguished from the reticular nerves, but which nevertheless are perhaps somewhat thicker, so to say coarser in outline, and in whose bundles at any rate a considerably larger number of medullated fibres are to be seen. The fibres in these trunks are also less numerous, and they chiefly ramify in the *outer* parts of the adventitia. Connections between nerves of this category exist, but they are few and far between and always consist of single fibres only, sometimes medullated, more frequently non-medullated; thus these nerves cannot be said to form any plexus. Some few times I have observed un-

questionable connections between these nerves and the *plexus adventitialis* of the reticular nerves, but these anastomoses are extremely few and, when they exist, are only formed of one single, non-medullated fibre, which connects greater trunks of the two species of nerves. The nerves here described nearly always divide *dichotomously*, at first at an acute, later on at an increasingly obtuse angle, and continue to divide, entwining the vessel cross-wise or obliquely to its axis in their course. After a shorter or longer course — very variable — these nerves terminate in *free endings*, always in the *outer* parts of the adventitia, most frequently in one of the following ways:

1) The termination most frequently met with in the vessels of the frog is the *free, knob-like ending*, the nerve, having attained a thickness of about $\frac{1}{2}$ —2 μ , terminating in a small, bulb-like knob about 1—4 μ long and $\frac{1}{2}$ —2 μ broad (*figure 1*). Even if these knobs look like endings, it is possible that the course of the nerve does not terminate here, the subsequent course only escaping demonstration through incomplete staining. As, however, I have again and again got identical results with the technic employed, I provisionally interpret them as nerve-terminations.

2) Sometimes the nerves are seen to terminate in or about spherical or oval bodies which are only faintly stained by methylene-blue. Of the nature of these bodies and the course of the nerves in or around them, I cannot assert anything worth recording — in the frog; typical *Vater-Pacini*-corpuscles I have never seen in this animal. The nerves do not continue on the other side of these corpuscles and probably end therein.

Smaller Vessels.

The best arteries in the frog for investigations like these I have found to be *a. palatina*, *aa. linguales*, *aa. mesaraicae* and *aa. dorsales pedis*. Even if the chromatophores give some trouble, it is always possible to recognise the arrangement of the nerves in these arteries as well as in the *aa. femorales* and *aa. crurales*. The innervation of these vessels is advantageously studied — in contrast to that of the aorta — after intracardial injection and subsequent staining on slides.

The innervation of all these vessels seems to be fundamentally identical. The only ones which differ are the *aa. mesaraicae*, the whole of whose innervation originates in the large nerve-trunks which entwine the vessels. The remaining arteries receive their nerves from the peripheral nerve-trunks, but in other respects the arrangement is the same: In good preparations it may be seen how these vessels receive medullated as well as non-medullated nerves which may be traced back to the surrounding nerves of the tissue. The nerves usually arrive at the vessel at an *acute* angle, frequently running

for some — often a long — distance peripherally with the vessel, while they were never observed to run centrally in this *first* part of their course. After having accompanied the vessel for a varying distance parallelly, quite close to it, the nerves begin to entwine the artery spirally and to connect with the other nerves on the vessel, reinforcing these. The vascular nerves frequently receive these reinforcements — *e. g.* in one instance (*a. cruralis*) one bundle in every 3—4 mm.

The arrangement on the vessel is the following: Around the vessel run one or two, about 5—15 μ thick, bundles of chiefly non-medullated nerves; these bundles are mutually connected by bundles of about the same thickness, these connections running obliquely over the vessel and being especially found in places where the whole diameter of the vessel separates the nerve-trunks. In this way a coarse mesh-work is formed, but the meshes are much smaller than those found on the aorta. At regular intervals other and thinner bundles are seen running obliquely across the vessel, and rather suddenly dividing into two or three branches — or at any rate *not* regularly dichotomously, the angle of division being nearly always acute. After a short course these branches divide again and through mutual connections form an astonishingly regular, true (anatomical) net-work, the rhomboidal meshes of which always run parallel to the axis of the vessel, and which are plentifully provided with nuclei of *Remak*, these being seen at nearly every point of division. These reticular nerves present a distinctly fibrillar appearance, and are of an astonishingly regular thickness, viz. 2—3 μ (*fig. 2*). This nerve-net lies distinctly *outside* the muscularis and, in place and arrangement, closely corresponds to the *rete interlamellare* described on the aorta. From this net, most frequently from the points of division, other non-medullated, finer ($\frac{1}{2}$ —1 μ) fibres penetrate into the muscularis, between the muscle-cells, and these are frequently touched in several places, in part by the same, in part by several different nerve-fibres. After a varying, often long and tortuous course, these fibres unite with others of the same kind and thus form a net-work, which is considerably more coarse-meshed than the interlamellar one, the length of the single fibre varying between *e. g.* 30 to 60 μ , compared with the 20—30 μ of the *rete interlamellare*; these figures vary to a certain extent in different arteries. *Free terminations* I have seldom seen, and these reticular nerves are the *only ones* I have been able to demonstrate in most of the vessels of this size.

This arrangement seems to be recurrent everywhere down to the quite small arteries (0.1 mm. in diameter), the only difference being that *the meshes in the nerve-net gradually become larger as the number of muscle-cells becomes less*.

The arrangement of the nerves on vessels with a diameter of less than 0.05 mm. must, however, be separately described. At a first glance it would seem that there is only *one* nerve-net on these vessels, but a close inspection

shows that there are still *two*. One runs between the muscle-cells exactly as is later to be described in the precapillary arteris; the second nerve-net can only be recognised as such when a certain stretch of the vessel is observable. A nerve-net is then seen, whose comparatively very long meshes are formed of bundles of nerves with only a few fibres — always non-medullated. These bundles entwine the vessel in a very long spiral, or for long distances run nearly parallel to it; the bundles are united by similar, very obliquely running bundles, which go off at a very varying angle (*fig. 3*). From this net, which is formed of nerves received by the vessel in the usual way, branches issue, which divide and unite with each other, thus forming *the muscular nerve-net* which is the only one to be seen in

the precapillary arteries (*fig. 4*). In these vessels, the muscularis does not form one continuous layer, the individual muscle-cells being separated by an interval — an interval which is gradually increased peripherally, the cells — as described by *Vimtrup* — lying more and more obliquely in relation to the axis of the vessel. Winding between these muscle-cells are seen non-medullated nerves, each only consisting of *one* single fibre, provided with nuclei of *Remak*, in part in their course, in part at the points of division where these nuclei may present a kidney-like appearance. In *fig. 4* muscle-cells, nerves, and nuclei of *Remak* are clearly to be seen. The meshes of the net are very longish, but here, too, the nerves form *a continuous network closed throughout* and connected in certain places with the nerves in the surrounding tissue and the nerves of other arterioles. This arrangement is continued down to

the capillaries. Frequently it is difficult to establish when the arterioles end and the capillaries begin. The least uncertain signs are the absence of the more or less obliquely placed muscle-cells, but this might be due to incomplete staining; besides, the course of the capillary is more tortuous, the arterioles often running quite straight through several fields of vision, and finally it is quite correct, as stated by various investigators, that the capillaries often divide at a comparatively right, the arterioles almost invariably at a more acute angle — but frequently one is in doubt, and all the more so since *the nerves of the arterioles continue directly in the nerves of the capillaries*, just as their arrangement here presents no fundamental difference. The aforementioned nerve-net on the arterioles is merely still more longish, but all the same it is easy to recognise it as a net. The nerves of the capillaries measure about $\frac{1}{4}$ — $\frac{1}{2}$ μ in thickness in the frog and are of a distinctly fibrillated appearance. The nuclei of *Remak* are not so frequently to be seen, but at any rate they are more numerous on the nerves of the capillaries in the frog than in other animals. Most frequently the nerve-net of the capillaries of the frog presents the following arrangement: Two fibres run in a slightly tortuous course on the capillary, one on each side; in several places the two

nerves approach each other, only to separate again just afterwards. These nerves are frequently seen to be connected through very obliquely running, somewhat thinner, fibres, which go off at an acute angle from the one nerve, then after a rather tortuous course joining the other nerve; in the places where such fibres arise a nucleus of *Remak* is often to be seen, but not always; sometimes an ovoid node is seen in the nerve in these places, one third or half the size of a nucleus of *Remak*, and in contrast to these not of a reddish hue, but of the same blue (in the fixed state, violet) colour as the nerve itself; sometimes these nodes are unstained in their centre, thus presenting the appearance of an *oval ring* — most frequently, however, they are compactly stained. Connections are frequently seen passing from the nerves of one capillary to the nerves of another one in the vicinity — but by no means always the nearest. Some few times such a fibre has been followed as far as 0,5 mm. and it then joined the nerves of a capillary of an entirely different system of arterioles.

In certain places the two nerves of the capillary are situated quite close together; it is especially in such places that one of them is seen to divide, and the three resultant nerves run on the capillary, interconnected through thinner fibres. More than three nerves are seldom seen on a capillary, and then only at the points of division.

The nerves of the capillaries are intimately connected with the nerves of the surrounding tissue; it is impossible to determine whether these connections are only simple anastomoses or whether the capillary nerves may be said to originate directly from these nerves — but one thing seems certain: *The nerves of the capillaries are connected centrally along the arterioles with the nerves of these vessels as well as with the peripheral nerves (see fig. 5).*

Nerves having free endings I have never seen on the capillaries any more than on the arterioles; on the other hand, it cannot be denied that such nerves *may* nevertheless influence these vessels. The fact is that *around* the capillaries and arterioles free, bud-like nerve-terminations are frequently found, and these sometimes bear a rather intimate relation to the vascular wall, being often separated therefrom by an interval of only 20—30 μ ; in a few places I have also observed a bundle of nerves twining round an arteriole for a short distance, only to leave it again to terminate in free endings in the tissue surrounding the vessel; in view of the theory of *Lewis* on the mode of action of the sensory nerves on the vessels, I cannot exclude a possible action of these nerves even on the small vessels on which they are not directly to be seen.

Nerves and Rouget-cells. As to this question I refer the reader to the chapter on *guinea-pig*, my best results being obtained with this animal, even

if the first preparation which furnished any evidence in this connection, was from the skin of the frog's *dorsum pedis* (fig. 6)*).

In this preparation — contrary to what usually happens — the *protoplasm* of the *Rouget*-cells was stained, even though faintly; the nucleus was as usual well stained and presented the characteristics described by *Vimtrup*; the size of these cells was about 20—30 μ , their form was oval and they were obliquely or parallelly placed in relation to the axis of the vessel. The nerves of the capillary in front of the *Rouget*-nuclei split into several fibrils, *all of which* — as far as I have been able to determine — united again on the other side of the nucleus. In spite of using very high magnifying power I have nowhere in the preparations seen free nerve-terminations, nor have I been able to determine whether the nerve-fibrils penetrate into the cell itself — as mentioned in p. 69 they do not seem to do so.

Venulae. These are seen to arise from the union of several capillaries, and here it is doubly difficult to determine when the vein begins and the capillaries end; the musculature is very sparse in the very small veins. Often, however, two or three capillaries are seen to unite into one larger vessel, and it would presumably seem unreasonable not to call this vessel a vein. The arrangement of nerves on these venules is just like that described for the arterioles, the meshes of the nerve-net being merely more longish and the nerves less numerous — but frequently no certain difference is seen. Again and again I have observed the capillary nerves continuing directly in the nerves of these veins — and in certain places in the skin of the frog I have been able to observe a seeming continuity between the nerves of the arterioles, the capillaries, and the veins.

Larger veins. The arrangement is fundamentally the same as on the arteries, the *interlamellar net* being of the same appearance as to the thickness of the nerves and the number of nuclei, but the meshes seem to be somewhat larger. The *muscular net* is distinctly more coarse-meshed than in arteries of about the same diameter, but otherwise no great difference is to be seen.

*) Dr. med. *Bj. Vimtrup* most kindly verified this preparation.

GUINEA-PIG

Large arteries (aorta, carotides, femorales, axillares). In the walls of these vessels there occur nerves which just as in the frog, may be divided according to their mode of ending into *reticular nerves* and *nerves having free endings*.

1. *Nerves which form nets in the vascular wall.* These nerves reach the vessels as large trunks containing medullated, but chiefly non-medullated, fibres, usually arriving at an acute angle. In the outer layers of the adventitia they divide — nearly always at an acute angle and nearly always into three or more branches — and in the outer layers of the adventitia they form continuous networks, composed of larger nerve-bundles in which a certain number of medullated fibres are to be seen. This net corresponds closely to the plexus later to be described as *plexus adventitialis* in rabbit and in man, hence it will not be described in detail here.

From this *plexus adventitialis* short branches, always non-medullated, proceed obliquely into the deeper parts; these fibres do not seem to anastomose before they form a narrow-meshed, rhomboidal network of non-medullated nerves, in places provided with nuclei of *Remak*, upon the muscularis, in the intermediary zone between this coat and the adventitia.

The fibres of this net have a thickness of about 8—12 μ , the nuclei average 20 μ in length and 10 μ in breadth; the length of the reticular fibres from corner to corner varies between 50 and 100 μ . The form of the meshes varies with the state of contraction of the vessel, the meshes being, however, nearly always placed parallelly to the axis of the vessel. A considerable difference exists between this net in the frog and the corresponding one in the guinea-pig; while thus nearly every single angle of the mesh in the frog presents a nucleus of *Remak* (*fig. 2*), these are far less numerous in the guinea-pig where 5—6 meshes without one single nucleus may often be seen. The fibres in this net, however, present the same fibrillar appearance in both animals.

Originating in this network, which, as to place, may be assumed to correspond to the *rete interlamellare* of the frog, single, non-medullated fibres, about 4—8 μ thick, pass into the muscularis, most frequently showing a very tortuous and oblique course between the individual muscle-cells, and here — as in the frog — they form a *true anatomical network*, the fibres

of which are still poorer in nuclei than those of the interlamellar net — often I only succeeded in discovering such a nucleus after some search. The form of the meshes here is far less regular than in the interlamellar net but the meshes *always* run in a transverse direction to the axis of the vessel. In this animal, too, the muscular net penetrates the *whole* of the *tunica muscularis*, becoming pronouncedly more coarse-meshed inwards towards the intima, the size of the meshes here being frequently as much as double the size found in the outer layers of the media.

While the nerves of the *rete interlamellare* still present a fibrillar appearance, the fibres of the *rete musculare* observed under a high-powered microscope present the same characteristic appearance as the corresponding fibres in the aorta of the frog. In a protoplasmic-like, faintly stained, homogeneous substance, rows of small, globular or oval, strongly stained, granules are disposed. The arrangement of these granules is remarkably regular; they are nearly always placed in the axis of the nerve. This picture of the finer nerve-fibres has previously been described by several investigators, and as to the cause why the nerves present this appearance several theories have been proposed; thus *Dogiel* thinks that these granules really correspond to parallel rows of granula in the nerve. *Allen*, however, thinks that the picture is an *artefact*, because, as he shows, a cylinder of fluid surrounded by a second fluid of another surface tension will be apt to "*break up in spherical drops*", and he supposes that nerves stained by methylene-blue will behave in the same way; in addition he shows that the thinner the cylinder of fluid, the quicker this structural change occurs. Be this as it may, one thing is certain, that the regular arrangement of the granula is much influenced by the time elapsing between the excision of the tissue and the staining; in tissue which is stained too late, the granula are quite irregularly disposed and more faintly stained — but this fact might be explained by both theories.

While thus all the nervous elements found in the vessels of the frog may be recognised in the vessels of the guinea-pig, in addition other elements were found in the vessels of this animal — nerves for which no analogue was found in the tissues of the frog. At first I wondered why vessels examined with the intima towards the observer did not seem to contain nerves in the innermost part of the vascular wall. True, the above-described muscular net was to be seen, but it was, so to say, glimpsed through the inner part of the muscularis. It turned out, however, that, when the preparations in question were examined under high magnifying power, fibres were observed, of the nervous nature of which I was gradually convinced. Originating in the intramuscular net, most frequently at the points of division, quite thin, protoplasmic-like fibrils run between the muscle-cells; these fibrils only present *one* single row of granules in the protoplasmic substance of which they seem to consist, and they have a remarkably regular course, not being tortuous like the fibres of the *rete musculare*, but on the contrary running relatively

straight throughout their course. The thickness of these fibres was always quite constant, about $\frac{1}{2}\mu$, and they did not become thinner in the innermost parts of the muscularis. Their length, too, was rather constant, about 10—20 μ , and each of these fibrils divided into only *two* branches — never more. The angle at the point of division was nearly always about right. As previously mentioned, these "*neuro-fibrils*", for so I think I may call them, originate in the intramuscular net, and bear a most intimate relationship to the muscle cells, frequently crossing these obliquely, *most frequently just opposite the nuclei of the cells*. I have never seen these fibrils penetrating into the muscle-cells, still less into their nuclei; when for a moment I thought I saw a fibre do this, after a more careful study I had to admit that the fibrils were probably extracellular after all. Nor have I succeeded in demonstrating differences in the appearance or the course of the fibril in the particular place where it crosses the nucleus of a smooth muscle-cell. Every single muscle-cell is frequently touched in several places by such fibrils, but, as mentioned above, it is *always crossed by one fibril opposite the nucleus*. On close inspection these fibrils were found in the whole of the muscularis, in the superficial as well as the deeper layers, everywhere originating in the intramuscular network. The individual fibril terminates by uniting with two corresponding fibrils and nowhere did I succeed in finding free nerve-endings; the system of neuro-fibrils permeates the whole of the muscularis from the outermost to the innermost part. As I supposed these fibrils to be of a nervous character (which supposition was fully proved by later degeneration-experiments) and as they always seemed to consist of one single, very thin fibre only, I termed them *neuro-fibrils* or *terminal fibrils*. I wish to emphasise, however, that I do not by these names mean to denote that these fibrils are the ultimate terminations of the vascular nerves (*see p. 88*), but merely that they are the ultimate ends of the vascular nerves *which I have been able to observe with the technic employed*.

2. *Nerves which terminate in free endings in the vascular wall*. Large medullated trunks containing several non-medullated fibres reach the vessel at an always large angle — most frequently at right angles to the axis of the vessel. Arrived in the outer layers of the adventitia the trunks start entwining the vessels spirally and simultaneously divide, always *dichotomously*. From these trunks issue branches, most frequently medullated, but with a slight admixture of non-medullated fibres, and these branches traverse the adventitia in the most varied ways — some continuing in the direction in which the nerves primarily reached the vessel, some running in the opposite direction, while frequently a branch divides in Y- or T-shape, one of the resulting branches running centrally, the other peripherally on the vessel. After a very tortuous, oblique course, during which the nerve may encircle the vessel several times, and during which course it continually divides *at an increasingly obtuse angle*, the branches end freely in the adventitia, often after having

attained a thickness of about $10\ \mu$, having lost their medullary sheaths. This, however, is not a quite constant finding: Sometimes it looks as if the nerve were non-medullated while later again it is seen to be distinctly medullated — but this might be due to incomplete staining and is only mentioned because this fact has previously been observed and described by *Dogiel*.

The free terminations of these nerves are usually provided with a little knob-like swelling at their extremity, about $5\text{--}10\ \mu$ long, and $3\text{--}6\ \mu$ broad. In some places the nerve seems to terminate in or around spherical or oval, pellucid bodies, of an average length of $0.02\text{--}0.06\ \text{mm.}$, always placed in the outer layers of the adventitia. In a few places the nerves seem to split up around or in such a corpuscle, forming a plexiform arrangement, in which I found it impossible to determine the termination of the individual fibres (*fig. 8 d*). In other places are seen structures, which correspond rather closely to the *Smirnow-Dogiel*-end-plates. In the guinea-pig I have, however, only seen these corpuscles a few times.

Besides these nerves the *nerves of the vasa vasorum* are seen on the vessels. The innervation of these vessels is quite similar to that described in the following. The nerves are freely connected with the nerves of the main vessel and in certain places it looks as if they directly originated in these.

Middle-sized and small arteries (aa. mesaraicae, numerous small arteries in bladder, muscles and skin). The arrangement is fundamentally as described under the large arteries. At a first glance it seems, however, as if only *two* of the nerve-nets described in these exist, but this is only due to the fact that the meshes of the *plexus adventitialis* are so large in relation to the diameter of the vessel that it may be sometimes difficult to recognise it as a plexus; on close inspection this plexus is always to be seen. In the smaller arteries, on the other hand, there seems to be no distinct separation between the *rete interlamellare* and the *rete musculare*; the former is not placed so definitely in one plane upon the media as in the larger arteries, but in spots it is drawn down into the media and in these places it merges into the muscular nerve-net without distinct separation (*fig. 7*). The nerves are of the same thickness as in the large arteries ($8\text{--}10\ \mu$ in the interlamellar, $4\text{--}6\ \mu$ in the muscular net) and preserve the same characteristics, the interlamellar net being chiefly distinguished by the nuclei of *Remak* (even though few) and the fibrillar appearance of the fibres, the muscular net by the far less numerous nuclei and the "protoplasmic-granulated" appearance of the nerves; further the course and direction of the meshes of the nets are invariably *across* the axis of the vessel in the muscularis, *parallel* to this axis in the interlamellar net. The *neuro-fibrils* too are of a quite identical appearance, thickness and arrangement. *Nerves having free endings* are seldom seen in arteries of this size; in the *crural artery* of the guinea-pig I have seen *up to 4 mm.* of the

vessel without these nerves and in the quite small arteries I have never seen nerves with free terminations; where they are to be found, especially in larger arteries (*i. e.* > 0.5 mm.), the arrangement of the nerves is quite identical with that described above, just as the fibres are of approximately the same thickness and end in the same ways.

Pre-capillary arteries. The course of the nerves in these vessels is exactly as described in the frog (*fig. 4*). A more frequent connection, however, seems to exist between the vascular nerves and the nerves in the surrounding tissue, and this is especially noticeable for the vessels in striped muscle.

Nerves having free endings I have never been able to demonstrate in these vessels; sometimes, however, nerves are seen which for a time run spirally round the vessel, without — as far as I have been able to judge — connecting with the vascular nerves, and these nerves *may* end in free terminations just *outside the vessel*, either in free, bud-like terminations, or in a fat cell.

Capillaries. Especially in the *amnion*, but also in the mesentery and in striped muscle (*diaphragm*) in embryos as well as grown animals, I succeeded in staining nerves on the capillaries.

Most frequently *two* nerves are seen on the capillary, sometimes running close together for long distances, more frequently separated by the vessel (*fig. 8*). Numerous anastomoses, usually very oblique, unite the two fibres, which at very varying distances are provided with nuclei of *Remak*; here also these nuclei seem typical of that kind of finer nerves which are yet of distinctly *fibrillar* structure, while the finer "*protoplasmic-granulated*" nerves, which frequently form the anastomoses, and which are sometimes the only ones on the vessel, are without any nuclei at all. Capillaries innervated in this way I have been able to follow for very long distances, especially in the *amnion* of the guinea-pig. *Nowhere* are free nerve-terminations to be seen, *the nerve-net is everywhere closed and continuous*. Through numerous anastomoses the nerves are united with the nerves of other capillaries — even with such as belong to quite a different arteriole. In many places, moreover, are seen connections with the other nerves of the tissue — this is especially true of the *capillaries of striped muscle*, while the innervation of the *amnion* and mesentery is very sparse, when the vascular nerves are excepted: Here and there a non-medullated nerve is seen, usually considerably larger and coarser than the nerves of the capillaries, provided with large nuclei of *Remak*, running for a distance of $\frac{1}{2}$ —1 mm. before it unites with a similar fibre. Free nerve-terminations as described by *Stöhr jun.* I have never seen on the capillaries. Nor are any freely terminating nerves at all to be seen on the arterioles or capillaries of the guinea-pig; even in this animal, however, it was noted — as in the frog — that these nerves

regularly terminated in the tissue *in the vicinity* of the vessels, and the possibility of their influencing the vessels cannot be excluded.

Nerves and Rouget-cells.

As mentioned above, my best preparations illustrating these conditions were prepared by staining the amnion and the mucous membrane of the bladder of the guinea-pig.

Good preparations were also obtained from numerous other tissues — especially the subcutaneous fat —, and I did not find indications of any fundamental difference in the capillaries of the various tissues, neither as to innervation nor as to *Rouget-cells*; also in the *subcutis of the guinea-pig* I saw cells, which quite corresponded to the cells described by *Vimtrup* in the frog. It was, however, necessary almost exclusively to study the innervation of these cells in *unfixed* preparations, the methylene-blue staining of nerves and of *Rouget-cells* not coinciding as to time, the nerve-staining being nearly always faded when the protoplasm of the *Rouget-cells* colours. True, the nuclei of these cells as a rule stain simultaneously with the nerves, but, as mentioned above, it is impossible from the nucleus alone to recognise a particular cell as a *Rouget-cell*.

I therefore proceeded in the following manner: Pieces from the amnion or mucous membrane of the bladder of the guinea-pig were stained in a watch-glass, which was kept swimming in a water-bath of about 40° (later on preparations covered with a cover-glass were stained in the incubator) and the preparations were examined as the process of staining proceeded.

In 10—15 minutes the large, coarse non-medullated nerves with nuclei of *Remak* mentioned above were usually well stained. In about 20—30 minutes the nerves of the capillaries were stained, and simultaneously the nuclei of these vessels; certain places in the preparations were now noted and a drawing was made of the course and relations of capillaries, nerves, and nuclei.

After the lapse of about 45 minutes the nerve-staining had usually disappeared; first the “protoplasmic-granulated” capillary nerves faded away, last — and frequently not quite — the large, coarse, non-medullated nerves which had no intimate connection with the capillaries. After about 60 minutes the protoplasm of the *Rouget-cells* was seen faintly coloured, simultaneously with the staining of the muscle-cells of the arterioles, and the staining now proceeded rapidly. It is therefore important to lose no time in entering the *Rouget-cells* on the previously executed drawing.

This technic has some drawbacks, especially that strong dry lenses have to be used, immersion lenses being unpractical, and in this way one can never be quite sure of the facts. I therefore tried to fix some preparations at the moment when the protoplasm of the *Rouget-cells* was just beginning to stain, and in this way I obtained a few preparations in which the protoplasm

of the *Rouget*-cells was well stained in certain places, simultaneously with a faint nerve-staining.

By both *modi operandi* identical results were obtained. When a nerve in its course reaches a *Rouget*-cell it seems to *divide into 3—6 finer fibrils*, which are remarkably like the "*neuro-fibrils*" mentioned above in thickness and appearance, and which — so far as I have been able to see — *all* unite again on the other side of the cell (*see fig. 22 a & b*). I have *never* succeeded in demonstrating free nerve-terminations here, and furthermore I have never seen one single picture which made it even probable that the nerve penetrated into the cell; in numerous preparations, on the contrary, it looked as if the protoplasm of the cell, when it stained, was so to say "turned away" from the place where the nerve had been observed. Several times, however, I have seen the nerve taking a course *across* nucleus as well as protoplasm (*figs. 22 a & b*), but I could never convince myself that the nerve penetrated into either protoplasm or nucleus — it only seems to lie close to but exterior to the cell.

Similar observations have not — as far as I know — been recorded. *Ioris*, however, mentions in 1906 that the nerves accompanying the capillaries in certain places seem to divide into a small "local" plexus, but he does not give any illustration of this, and he obviously did not dream of the existence of muscular elements on the capillary wall.

That the cells which I have observed *really are Rouget-cells*, I have no doubt; it might perhaps be supposed that the cells in question were the "*lemmoblasts*" of *Held*, but these cells are considerably smaller. On the other hand, I wish to stress *that as to the course of the nerve across the nuclei of the Rouget-cells (figs. 22 a & b) doubt may be entertained*; any one who has worked at vital staining with methylene-blue will know that *e. g.* red blood corpuscles have a tendency to absorb the dye (because of this fact nerves on a thin-walled vessel filled with corpuscles frequently do not stain); certain nuclei, and of these especially the nuclei of the *Rouget*-cells exhibit the same tendency. It is therefore possible that the relation of the nerve to the nucleus of the *Rouget*-cell is *not* as described above, the picture described being produced by *incomplete staining* of that part of the nerve which lies in intimate relation to the nucleus, the latter absorbing the dye. Whether or not this is the case I cannot decide — but the intimate relationship of nerve and *Rouget*-cell cannot be doubted*).

Small veins. These vessels present an identical arrangement to that described in the frog. Everywhere the nerves are continuous with the nerves of the capillaries from which the veins are formed, and these relations are

*) As previously mentioned, the modern investigator of the *Rouget*-cells, *Dr. med. Bj. Vimtrup*, has most kindly verified my first preparations. E. B.

preserved upwards to the larger veins. The arrangement is the same as in the corresponding arteries, but in a few places I am sure that I have seen *free nerve-terminations on the walls of the veins* — an arrangement, which seems more frequent in small veins than in arteries of corresponding diameter.

Larger veins. In its broad features the arrangement of the nerves is similar to that of the arteries. The fibres from the very broad-meshed *plexus adventialis* continue in a very oblique course to the muscularis, where they divide, without, however, forming any proper *rete interlamellare*, but more directly merging into the *rete musculare*. The thickness of the fibres and the arrangement here are much as the corresponding relations in the corresponding arteries, but, in accordance with the irregularity of the arrangement of the muscle-cells, the course of the fibres is quite irregular: The nerves run in and out, backwards and forwards, in all planes. The size of the meshes is also, perhaps, somewhat larger than in the corresponding arteries, and in any case much more variable. Just because of the less number of muscle-cells the course of the fibres in the vascular wall is easier to trace, and very often beautiful pictures are seen, but even with these good conditions I never succeeded in demonstrating free nerve-terminations in the muscularis.

Nerves having free endings are found in the walls of the larger veins, but only in the adventitia, and seem less numerous and more scattered than in arteries of the same size. I have several times substantiated connection between these nerves and sensory corpuscles *outside* the vascular wall, but in the guineapig I have never succeeded in seeing these corpuscles in the walls of the veins. This, however, is not true for the *vena cava inferior*, whose wall on the contrary seems abundantly provided with freely terminating nerves as well as with the above-described spherical or oval end-corpuscles.

RABBIT

Notes. In addition to what stated in the chapter entitled *Technic*, I shall emphasise in this place that for rabbits and larger animals it is necessary to divide the walls of the larger vessels; while most of the tissues of the guinea-pig become sufficiently pellucid by clearing in glycerine, the vessels of rabbits and larger animals are too thick and compact for this. To obtain a better idea of the nerves in the deeper layers of the arterial wall, it is therefore necessary to denude the vessels of the adventitia; this is usually easy in the fresh, easier still in the fixed preparations, due to the macerating influence of the picrate of ammonia; the adventitia should be removed as a continuous layer; it is then divided into suitable pieces, some being mounted with the inner, some with the outer side upwards. The rest of the artery, the muscularis and the intima, are in the same way mounted with respectively the outer and inner side upwards, and are sufficiently pellucid after being treated in the picrate-glycerine-mixture for 1—2 days. The whole of the arterial wall may be examined in this way.

In addition, I have several times, by keeping the tissue for some time (up to one week) in the picrate-glycerine-mixture, been able to examine the whole of the vascular wall in *one* preparation, the preparation being squeezed between two large slides by means of two small clips for about 24 hours, the result being that, even in these animals, the course of the nerves in the vascular wall may be studied in continuity in *one* preparation.

Material. Nearly all the larger arteries have been examined: the *aorta*, *carotides*, *axillares*, *femorales*, *renales*, *mesaraicae*, *pulmonales*. With a view to later degeneration-experiments special attention was paid to the *auricular vessels*. Numerous smaller arteries from the *extremities*, *intestines*, *heart*, *skin*, *peritoneum*, *diaphragm*, *cornea* have been examined; of the veins the *vena cava inf.* and in addition the veins of most of the arteries mentioned.

As to the innervation of *the larger arteries* (*the aorta* and its branches, *axillares*, *femorales*, *mesaraicae*) it was found to be fundamentally the same throughout. Upon a cursory examination one might be led to assume a fundamental difference between the innervation of the *visceral* arteries (*e. g. renales*, *pulmonales*, *mesaraicae* etc.) and the peripheral arteries of the *extremities*. The difference, however, is only apparent; it looks as if the visceral arteries are much more abundantly provided with adventitial nerves — the *renalis e. g.* is quite entwined by large bundles of medullated as well as non-medullated nerves, and these bundles divide and re-unite upon and in the adventitia of the vessel. It might therefore look as if the *plexus adventitialis* was extraordinarily rich in these vessels, but if the vessel is followed in its course, it becomes apparent that the greater part of the nerves continue

as large trunks into the hilus of the kidney, there escaping further examination. It would, however, seem reasonable to infer that these nerves are *not vascular nerves sensu strictiori*, but only nerves which accompany the vessel for some distance, later on separating from them to pass on to their fields of innervation in the organs themselves. If the adventitia is peeled off such a vessel, the picture thus revealed of the deeper nerves is moreover quite identical with the picture of any other artery of equal diameter.

The picture of the innervation of the large vessels is monotonously the same as that described for the guinea-pig and later to be described in man, and shall be treated very briefly in this place. It *ought*, however, to be described, if only to demonstrate the far-reaching parallelism of the innervation of the blood-vessels in different animals. In the rabbit, too, the nerves of the blood-vessels may be divided into nerves ending in nerve-nets within the vascular wall, and nerves ending in free terminations.

1. *Reticular nerves.* The *plexus adventitialis* of the rabbit lies in the outer layers of the adventitia and is formed of large nerve-trunks which reach the vessel at an acute angle. The trunks on the *aorta* may be as much as 1 mm. in thickness, and the bundles of all vessels, besides the numerous non-medullated nerves, contain some medullated fibres. Characteristic of the course of these nerves in the adventitia is the occurrence of *large* anastomoses between *large* nerve bundles (fig. 9); but, in addition, numerous connections by single, coarse, non-medullated fibres provided with large nuclei of *Remak* are to be seen.

From this plexus bundles of 4—5 fibres penetrate deeper into the adventitia, without anastomosing or dividing in their course. Only in the intermediary zone between the adventitia and the media do they break up into always non-medullated nerves and form the *rete interlamellare* (fig. 10), which here too is disposed parallel to the axis of the vessel, and which — as in the guinea-pig — is only sparsely provided with nuclei; while the individual fibre in the guinea-pig is still distinctly *fibrillar* in appearance, this is only the case with the *thicker* fibres in the corresponding nerve-net in the rabbit; the main part of the nerves present the characteristic "*protoplasmic-granulated*" appearance typical of the *rete musculare* of the guinea-pig. The meshes of the *rete interlamellare* in the rabbit are most frequently *rhomboidal*, but may be square; the length of the individual fibres is 100—150 μ compared with the 50—100 μ found in the guinea-pig, and the net also seems more coarse-meshed. The thickness of the fibres varies between 5—10 μ ; the nuclei of *Remak* are very few, they measure about 15—20 μ in length, and about 10—15 μ in breadth.

From the junctions of this nerve-net, 2—4 μ thin fibres pass obliquely into the muscularis and here — as in the guinea-pig — they form a narrow-meshed *rete muscularis* whose meshes always run transversely to the axis of

the vessels. The individual fibre is about 15—30 μ long, about 1—3 μ thick, and is only distinguished from the fibres of the interlamellar net-work by the fewer granula placed in the protoplasmic substance — but as previously mentioned, this seems a general rule as the nerves grow thinner.

In the vessels of the rabbit also these nerves seem to stop before reaching the intima, and from this point inwards only the "terminal" *neuro-fibrils* are seen, here also of exactly the same thickness throughout, about $\frac{1}{4}$ — $\frac{1}{2}$ μ , and presenting the same protoplasmic appearance as described for the guinea-pig. Here, too, the neurofibrils form *one* continuous net, pervading the media, and the meshes in this net do not seem to become larger towards the intima, — as in the intramuscular net.

I have never succeeded in seeing nerves in the intima of the rabbit any more than in that of the guinea-pig.

2. *Nerves having free endings.* These nerves are present in all larger vessels. Again and again they may be followed back to peripheral nerve-trunks and as large bundles they reach the vessel at a less acute angle than the reticular nerves — frequently almost at a right angle (*fig. 11*). These trunks certainly contain a few non-medullated nerves, but the bulk is formed by medullated fibres, which preserve the medullary sheath for a long distance, frequently even to their end. Arrived at the vessel the nerves immediately begin dividing, nearly always dichotomously, at an increasingly obtuse angle at the points of division as the nerve becomes thinner. This is also to be seen in the very frequent places where a large nerve trunk gives off a small branch, which shortly afterwards terminates freely (*fig. 11*). During its course the nerve often entwines the vessel spirally (*fig. 12*), continually giving off branches. The nerve itself — like the branches — ends freely in the *outer* layers of the adventitia; I have never — as *Dogiel* asserts he has — seen these nerves in the media or even in the deeper layers of the adventitia. As previously mentioned, the nerves preserve their medullary sheaths for a long distance, but sometimes it may look as if the nerve was for a time non-medullated, later on regaining its sheath.

In the rabbit the *mode of ending* of these nerves varies very little: A few nerves end in the same pellucid, indeterminable structures described in the guinea-pig; more frequently I have found the structures described first by *Smirnow*, later by *Dogiel*, as *sensory end-platelets* — the nerves splitting up into a characteristic structure resembling a cluster of grapes or a branch of ivy in which it is impossible to follow the course of the fibres; like *Dogiel*, I have frequently seen these structures placed freely in the adventitia without any capsule; more often still they seem to be surrounded by a pellucid, structureless membrane, which sometimes follows the irregular outline of the end-corpuscle, while sometimes it seems to encircle the whole of the structure as a regular oval or more seldom a round capsule. Frequently several such

structures may be seen on a single nerve, and the nerve is moreover nearly always medullated in the places from which the end-corpuscles spring. These corpuscles I have observed varying between 0.06—0.2 mm. in length, the breadth being much more variable — sometimes the whole structure is somewhat like a stripe, sometimes it expands, being as broad as it is long. Between two such corpuscles I have *once* seen a connection by a single non-medullated nerve, provided with large nuclei of *Remak*, but this seems to be a rare exception, and I cannot confirm *Dogiel's* observation that these bodies often give off nerves which make new corpuscles.

In a few places branches from these nerves seem to end in a little, *knob-like, free swelling*, a little larger than the thickness of the nerve; these nerves, however, are nearly always non-medullated, and I cannot exclude the possibility of incomplete staining in these places — so much the more as these “endings” are infrequent in my preparations of the rabbit.

More rarely than in the *Smirnow-Dogiel* corpuscles a medullated nerve may end in such a way that its ultimate, numerous ramifications are interlaced, forming a structure which resembles the “*comets' tails*” of various investigators; these structures I have always found composed of fine *non-medullated* fibres, and they always seem to lie parallel to the axis of the vessel, the *Smirnow-Dogiel*-endings more frequently lying across or obliquely to it; the individual fibres in the “comets' tails” always seem to end freely.

As to the *distribution* of these various “*sensory end-corpuscles*”, they are numerous on the aorta and, in short, on all larger vessels, including the larger veins. Just as the freely ending nerves themselves they seem to be more rare as the diameter of the vessels diminishes and on *vessels under 0.2 mm.* in diameter (*fig. 13*) I have only seen them as rare exceptions in the rabbit and then at large intervals — as much as 0.5 mm. On the arterioles and the capillaries I have never seen such structures, nor nerves having free endings, which seem to be reserved for larger vessels.

I have also observed connections between these and the reticular nerves in the rabbit, but here too they only exist as single non-medullated fibres — *never* as larger bundles. Nor do the freely terminating nerves exhibit frequent anastomoses among themselves, and in the rabbit I have not even seen connections by single fibres.

The arrangement here described of the vascular nerves in the main holds good down to the quite small arteries, but in these only *two* sure nerve-nets can be distinguished — the *adventitial* plexus, which resembles that described for the corresponding vessels of the guinea-pig (with very large “meshes”, *i. e.* the “plexus” is reduced to two or three bundles which at large intervals intercommunicate by bundles of equal thickness to themselves), and a *combination of the muscular and the interlamellar nets*; this latter is distinct in

places, but in numerous places the adventitial plexus merges directly into the muscular net. The fibres themselves present the same characteristics and about the same thickness throughout — notably the fibres do not seem to diminish in thickness with the diameter of the vessel. There seems to be no reason, then, for describing separately the innervation of these vessels, it will suffice to refer the reader to the corresponding chapters for *man* and to *fig. 14*.

Arterioles. While I did not succeed in demonstrating *nerve-cells* in larger peripheral arteries, I found such cells in *precapillary arteries* — but only on such vessels as belonged to the *visceral system* (*fig. 15*). These small nerve-cells, it seems, are especially to be found in the places where the vessel loses its muscle-cells, and where it divides into branches, which one would be inclined to call capillaries. I have seen such nerve-cells, judging from their appearance *sympathetic* nerve-cells, on the arterioles in various different tissues, most frequently perhaps in the fat capsule of the kidney, but this may only have been accidental.

For the rest the arrangement of the nerves of the arterioles of the rabbit does not exhibit any new particulars beyond those previously described. *Fig. 4* (from *frog*) may be used as an example; there is the difference, however, that in the rabbit finer fibrils, in appearance identical with the *neuro-fibrils* described, are frequently seen as connections between the larger nerves of the arteriole; these larger nerves themselves are most frequently of a distinctly *fibrillar* appearance, and nuclei of *Remak* are more frequent than in the larger vessels. These nerves are directly continuous with

the nerves of the capillaries. Here, also, the picture resembles the relations known from the frog and the guinea-pig. The fibres are perhaps a trifle tinner, but the arrangements is identical. In preparations from this animal also, no nerves having free endings are to be seen on the capillaries, the same continuously closed nerve-net being found throughout; the meshes are perhaps a trifle coarser than in the guinea-pig (*fig. 16*).

In the rabbit, too, I succeeded in staining *Rouget-cells* and nerves simultaneously in a few preparations, but the investigations did not furnish any new facts. Here, too, the neuro-fibrils nowhere seem intracellular, and all the fibrils in the little "local" plexus opposite the *Rouget-nucleus* seem to reunite on the other side of the nucleus (*fig. 22 a & b*).

Veins (*fig. 17*). The veins, small and large, present the same picture as in the guinea-pig. In this animal the freely terminating nerves with their typical endings seem, however, to occur considerably more peripherally than in the arteries. Where they are to be seen, they present the same appearance and are found in the same places as in the arteries.

MAN

Notes. The material of course must be rather casual inasmuch as it is confined to tissue removed by surgical operations. In spite of various experiments on reactivating the nerves of dead tissue in different ways, I have not succeeded in getting even a trace of specific nerve-staining with methylene-blue — the tissue is stained diffusely. By the kindness of various surgeons*) I have, however, collected enough material to get a sufficiently clear understanding for my purpose of the morphology of the nerves of the blood-vessels in man.

The *technic* of course has to be changed to a certain extent, it being impossible to stain nerves by injection in the living organism. I have successfully tried injection into amputated extremities, but when I had developed the modification previously described, I obtained such good results that the injection, which is frequently difficult, and which often cannot be executed as soon after the removal of the tissue as desirable, could be entirely dispensed with. Immediately after the removal, the tissue was placed in a *Dewar*-glass in which the usual solution of dye was kept at about 38°, and here it survived until the further processes could be carried out; these were then performed in the usual way (*pag.* 46).

The nerves of the large arteries. Of these vessels the following were examined: *Aa. renales, axillares, femorales, profunda femoris, poplitæa, brachiales*. In the preparations of the *adventitia* mounted with the outside towards the observer, numerous large, as much as 2 mm. broad, nerve-trunks are seen upon the *adventitia*. Especially the *renal artery* exhibits a surprising abundance of large trunks with medullated as well as non-medullated nerves, which divide on the vessel and are united by large branches; to a very large extent, however, these nerves may be only *accompanying nerves*, which certainly give off branches to the vessels, but whose main part is destined for other organs. Relations on the arteries of the extremities are more simple. On these, too, large bundles, frequently 1—2 mm. broad, are to be seen in the *adventitia*, but the complete network of large nerve-trunks seen on the visceral arteries, is not found here. In man, too, the nerves of the blood vessels may be divided into *two groups* according to their manner of termination: The *reticular nerves* and the *nerves having free endings*.

*) Thanks are especially due to my former chief, Dr. med. J. Ipsen, Chief Surgeon of the State Hospital, Sønderborg.
E. B.

1. *The reticular nerves.* These nerves usually arrive at the vessels at an acute angle and for a time run peripherally with the vessel before they begin to divide in large bundles, which may now run centrally as well as peripherally on the vessel, meanwhile anastomosing with each other as well as with the other nerves of the vessel. The conspicuous feature of these anastomoses is their size, the connecting bundle being of the same thickness as the main trunks (*fig. 18*), and so in man, too, one may speak of a real *plexus adventitialis*. Besides these large anastomoses the nerve-bundles are connected by coarse, single, non-medullated fibres provided with large nuclei of *Remak*; such fibres also in certain places connect the *plexus adventitialis* with the *freely ending nerves* later to be described, but neither in man — nor in any of the animals examined — have I found evidence of a *common* plexus formed by union of the two groups of nerves. Even if a medullated fibre is seen now and then, the bundles of nerves here described are quite dominated by non-medullated nerves, and this is the case in an even higher degree in man than in any of the animals examined.

In addition to the adventitial plexus the *nerves of the vasa vasorum* are to be seen; according to their size these vessels are provided with nerves which may vary from a close network to an arrangement resembling that of the capillaries (*fig. 18*); these, also, may be seen in the preparations, but their innervation is not different from that to be described later. It should perhaps be noted, however, that the *vasa vasorum* do *not* seem more abundantly provided with nerves than might be expected from the size of the vessels — as asserted by some investigators.

Originating in the *plexus adventitialis*, branches, always composed of several, always non-medullated, nerves of a distinct fibrillar appearance, pass obliquely through the adventitia, seemingly without dividing or anastomosing in this part of their course. In the inner part of the adventitia, however, these nerves suddenly divide, and in preparations of the adventitia mounted with the inside towards the observer, the nerves are seen to be considerably thinner than on the outside: *they have divided* and are much more numerous. Even in these preparations an indication of the nerve-net later to be described may be seen (pieces, which adhere to the adventitia, and were left there when this coat was stripped off), but this net is only seen in its entire extent on the outside of the stripped muscularis.

In well-stained preparations of the *muscularis* mounted with the outside towards the observer, a broad-meshed nerve-net is seen immediately upon and external to the muscularis (*fig. 19*). In some places part of the adventitia is left upon the muscularis, and in such places the afferent nerves may be seen breaking up in thinner branches and forming the plexus through connections with each other.

In man as in the animals, this nerve-net is undoubtedly a *true, anatomical nerve-net*, in the sense that all the nerves are continuous with each other,

but the form of the meshes may vary to a certain extent — obviously with the degree of contraction of the vessel; frequently this net also in man exhibits the typical rhomboidal meshes, parallel to the axis of the vessel; in other preparations the meshes may be nearly square, but I have never seen them placed transversely to the axis of the vessel. The nerves forming this *rete interlamellare* present the same "*protoplasmic-granulated*" appearance as described for the corresponding nerves in the rabbit; the fibres perhaps seem a bit more flattened, the breadth being rather regular, most frequently $4-8\ \mu$. The length of the individual fibre (the sides of the meshes) is most frequently $90-150\ \mu$, but as previously mentioned, it may vary within rather wide bounds. *Nowhere are free nerve-endings to be seen.* In certain places especially at the junctions, the fibres are provided with nuclei of *Remak*, about to the same extent as in the rabbit, the nuclei being much less numerous than in the frog. As will be seen by the figures mentioned, the *rete interlamellare* in man seems to be considerably more coarse-meshed than in the animals; this was found for all the larger human vessels examined.

From the interlamellar net thin nerves, with astonishing regularity measuring $2-3\ \mu$ in thickness, and seemingly consisting only of one single, always non-medullated, fibre, go deeper, most frequently originating at the junctions of the interlamellar net. These fibres are always *without any nuclei at all* and wind obliquely inwards between the individual muscle-cells; after a course measuring rather regularly $30-40\ \mu$, every fibre divides into two, usually at an angle of $60-90^\circ$; every one of the resulting fibres again divides into two (*fig. 20*) in the same way, thus for the second time in the vascular wall forming a true anatomical nerve-net: the *rete musculare*, which seems to penetrate to rather great depths, the fibres running around and between the smooth muscle-cells, without, however, exhibiting any constant relationship to them. In human preparations this nerve-net, too, seems closer in the outer parts of the media, and in preparations mounted with the intima upwards, this net is only indistinctly seen — as through a mist, even when the endothelial layer is removed. In such preparations the only nervous elements, which are present in the inner part of the muscularis, seem to be the *neuro-fibrils*. These originate in the fibres of the muscular net, at the junctions as well as in the course of the fibres themselves, frequently several neuro-fibrils from the same fibre. These neuro-fibrils always show a constant diameter, $\frac{1}{4}-\frac{1}{2}\ \mu$, and, examined through powerful objectives, reveal a *single* row of small, faintly stained granula, placed in a thin, protoplasmic-like substance; seen at less magnifications the fibril presents a nearly linear appearance. The neuro-fibrils, too, divide, but at a rather varying angle, from $45-120^\circ$, and they wind in between the muscle-cells in such a way that at any rate always one neuro-fibril touches the cell opposite the nucleus; besides by this one fibril, the cell is frequently touched in other places by several other neuro-fibrils. The whole of this

picture is frequently difficult to unravel in the walls of the larger arteries, and I must therefore be content to assert that, *in my opinion*, the neuro-fibrils in the large vessels of man do not end in free terminations, but in a *continuous, extracellular nerve-net*.

The nerve-net formed by the neuro-fibrils seems to pervade the whole of the media and in preparations divested of the endothelial layer the individual neuro-fibrils are often seen lying free on the surface of the preparation. Hence, there can be no doubt, it seems, that in human vessels, too, the innermost parts of the muscularis contain nervous elements.

I have found no evidence whatever to warrant a division of the nerve-nets of the vascular wall in *zones* which might perhaps appertain to different neurons. It cannot, of course, be demonstrated that the nerve-nets really, without any break at all, pervade the whole of the media from the origin of an artery to its end, a limit being fixed by the length of the preparation which can be examined; I have, however, examined preparations which show the nerve-nets without the least break for a distance of 3 *cm*. I therefore suppose that the nerve-nets described continuously pervade the whole of the muscularis.

2. *Nerves having free endings*. Besides the reticular nerves, other nerves may be seen in the preparations of the adventitia; they, however, are much less numerous than the reticular nerves and they seem to present a coarser appearance, containing far less fibres in their bundles. These trunks are chiefly composed of *medullated nerves*, though some non-medullated are always present. They usually reach the vessel at a large angle, across its axis or nearly so, and now start to entwine the vessel spirally. After 1—4 spirals, during which course branches are constantly given off, these branches running down across the vessel, the nerve finally divides rather suddenly into numerous branches, always *dichotomously*, the angle between the branches becoming increasingly open, at last frequently 180°. The modes of ending of these nerves quite correspond to the modes mentioned for the rabbit: *They always end freely and always in the outer layers of the adventitia*. The terminations themselves may be of differing appearance:

1) In human vessels the termination most frequently met with seems to be the "*sensory*" "*end-platelet*" first described by Smirnow and Dogiel in cats and dogs, later on by Ioris in man. The nerve having divided a certain number of times (frequently 5—6, sometimes more, now and then far less), it ends, most frequently still medullated, in a complex convolution of ivy-like structures, all of them lying close to each other, and being frequently enveloped by a quite thin structureless capsule, which in some measure follows the irregular form of the end-corpuscle. These corpuscles are always placed in the *outer* layers of the adventitia — always a little below the surface. The form of the platelets in question may vary to a great

extent; frequently the platelet is *oblong* (it may lie parallel to, or more often transversely or obliquely to the axis of the vessel), now and then it is more circular, but in every case it looks *as if the platelet lies in one plane* — it does not seem to possess any extension in depth worth mentioning. The individual ivy-like structures are interconnected by fibres, which, of whatever nature they may be, at any rate are *not* medullated nerves, but as previously mentioned the whole structure is so complex that further particulars cannot be studied in the thick preparations.

The *size* of these corpuscles may vary a great deal; most frequently they are 0.05—0.1 mm. long, and 0.01—0.05 mm. broad, but frequently structures are seen which are far smaller, but which plainly exhibit the same structure.

In some places I think I have seen these bodies without any distinct capsule (which *Dogiel* takes to be the rule), but these are exceptions. The distribution of these *Dogiel's* end-bodies in the vascular wall seems very irregular; frequently there seems to be a collection of them in certain places, in other places they are not seen at all (*incomplete staining?*). On the other hand, I have not been able to find any fundamental difference in their number in various larger arteries — more especially I have found neither more nor less in the visceral arteries than in the vessels of the extremities.

Dogiel thinks that these "sensory" end-bodies are very numerous, as he often saw many in the same field of vision. Further he saw them lying in different planes in relation to each other in the vascular wall, and he found that non-medullated nerves might originate in one body, and after a short course form another body. Lastly *Dogiel* thinks that the nerve which carries the end-corpuscle is most frequently non-medullated in the blood-vessels, being medullated in the pericardium and elsewhere.

These assertions I am not able to confirm. I have never seen more than *e. g.* two platelets in a 0.1 mm. length of arterial wall, nor have I seen the bodies lying in different planes in relation to each other; and I have never seen connections between different bodies. Finally, several of my best preparations distinctly show that the nerve which carries the end-corpuscle is most frequently medullated in the vascular wall, too, — as is also maintained by *Hirsch* — the nerve being only non-medullated in a few cases and for a short distance; this might be due to incomplete staining.

2) The nerves having free endings may — but only in large vessels — end in oval or more spherical bodies, nearly pellucid after fixation; they seem, however, to reveal a distinctly lamellar structure; these bodies vary in size between 0.1—0.5 mm., and the afferent nerve is always medullated (*fig. 22 d*). Several times I have, moreover, seen a thin non-medullated nerve — most frequently in fresh preparations — (I have never been able to ascertain where these nerves originate) which also seemed to end in the bodies in question; the bodies themselves I have supposed to be the *Vater-*

Pacini-corpuscles discovered in the vessels by *Thoma* and later found by several investigators. These bodies are not numerous in the vascular walls, and invariably lie in the outermost parts of the adventitia; still more frequently they are placed a little *external* to the adventitia, but even then they may be provided with a nerve whose other branches end in the vessel. Moreover, I have seen spherical bodies, varying in size from 0.05 to 0.1 mm., in which the nerve seems to end in a complicated convolution.

Of the *intracapsular course* of the nerves in these two forms of end-bodies I can assert nothing worth recording; frequently the nerve seems to form a complex convolution which sometimes may be placed as a narrow nucleus in the end-body, sometimes may extend in numerous bends and coils, frequently provided with quite irregular swellings, which may be connected by thinner fibres (*fig. 8 e*).

3) Several freely ending nerves seem to end in the "*free, knob-like endings*" of all authors; these "endings" I have doubted to a certain extent — the "ending" might be due to incomplete, interrupted staining. These "knobs" are, however, also present in my preparations, and are often seen in nerves whose other branches end in typical sensory end-bodies. The difference between *Dogiel* and me as regards the number of sensory platelets might then be explained as incomplete staining of my preparations. I have, however, never been able to follow the subsequent course of the unstained nerve from the "knob" — and with sufficient magnifying power this is nearly always possible, if it is only a case of incomplete staining. At a point, at which, from the diameter and angle of division, the nerve might be expected to end in a sensory end-corpuscle, it suddenly stops, very frequently just after having divided at an angle of about 180° , and *both* of the branches end in a little, oblong knob. I have *never* seen one of the branches end in a *Smirnow-Dogiel* body, the other in a knob-like ending.

Other forms of free terminations I have sometimes seen — also the "*comet's tail*"-like structures of various investigators. These, however, seem to be rare in human vessels — they are always placed along the axis of the vessel.

Nerves having free endings I have never found deeper in the vascular wall than the adventitia, and as previously mentioned, most frequently in the outer parts of this coat; like *Hirsch*, I, too, am unable to confirm *Lapinski's* and *Glaser's* sensory nerve-endings in the muscularis.

Smaller arteries (radialis, ulnaris, tibialis, peronea, numerous arteries of muscles, fat, skin, peritoneum etc. with a diameter of up to 0.5 mm.). The arrangement is on the whole identical with that described for the larger arteries; more especially no difference is found in the "intensity" of the innervation, neither more nor less nerves being seen in each field of vision than in the largest arteries.

The number of nerves having free endings, on the other hand, is considerably diminished as the vessels become smaller of diameter, and I have never found them ending in *Vater-Pacini-corpuscles* on arteries under 2 mm. in diameter. The *Smirnow-Dogiel-platelets* I have seen on arteries of 0.5 mm. diameter, never in smaller vessels. On the other hand, nerves having free endings are often seen arranged around the human precapillary arteries and the capillaries themselves, frequently only 20—30 μ from the vessel; in the *subcutis*, moreover, the sensory nerve-plexuses are frequently found in near relation to the small arteries, and as far as the histological evidence goes, it is quite possible that these nerves may influence these vessels, as discussed at p. 61.

Arteries smaller than 0.5 mm. (examined especially in *hernial sacs*, *muscles*, *skin*). While the arrangement of the nerves in the vascular wall is the same down to vessels of about $\frac{1}{2}$ mm. in diameter, the nerve-nets in still smaller vessels are more difficult to distinguish from each other. While it is still possible to speak of an *adventitial nerve-net* in so far as larger (*e. g.* about 50 μ broad) bundles of non-medullated nerves are seen on the vessels, connected by nerves of about the same thickness as the bundles themselves, the *interlamellar net* and the *muscular net* begin to merge into each other, the interlamellar net being at first drawn deeper in certain places only to be gradually completely merged in the muscular net; still thicker fibres may always be distinguished, which provide the muscular net in which the neuro-fibrils originate, and these fibres anastomose. While the fibres of the interlamellar nerve-net (or rather the fibres which provide the muscular net) always decrease in diameter with the diameter of the vessel, the diameter of the fibres of the muscular net and the thickness of the neuro-fibrils are invariably the same as found even in the largest arteries. In this fact, too, one may see a hint that the said elements are some of the most extreme branches of the nervous system.

On the *precapillary arteries* the nerves are reduced to two or three bundles of nerves, each composed of three or four, 10—20 μ thick, fibres, which run along the vessel and anastomose; from these bundles the *neuro-fibrils* proceed directly to the muscle-cells, these no longer forming a continual layer but being separated by an ever increasing interval; at the same time these cells lie more obliquely on the vessel. Most favourable to the study of the mode of innervation are such precapillary arteries, in which the interval between the cells is about 4—5 times the breadth of a smooth muscle-cell (*fig. 22 c*). Here, with high magnification, the neuro-fibrils may be seen to proceed from the coarser bundles, run to the individual muscle-cells, and when — as is frequently the case — the muscle-cells are placed with the nuclei alternately on one and the other side of the vessel, the neuro-fibril,

always one single neuro-fibril, may be seen running from one muscle-cell to another, crossing the vessel every time in its course in order to touch the cell opposite the nucleus; after having supplied 4—5 muscle-cells, the neuro-fibril again bends back in one of the nerves, at an acute angle, another neuro-fibril starting a similar course. Morphologically I have not been able to get any nearer to solving the problem of the possible innervation of the smooth muscle of the vascular wall; *I have never seen intracellular, nor intranuclear endings*. Even with very high magnification I have only been able to confirm *that the nerve passes the nucleus of the muscle-cell seemingly extracellularly and without dividing*; but on the other hand *I am quite sure that the neuro-fibril really continues on the other side of the nucleus*, and equally sure that the neuro-fibril after having provided a varying number of cells *really again joins one of the accompanying nerves, not having lost in diameter during its course*.

Innervation of human capillaries. The nerves of the human capillaries, also, are directly continuous with the nerves of the arterioles. The nerves present the typical "*protoplasmic-granulated*" appearance and on the whole correspond to the corresponding nerves of the guinea-pig (*p.* 67). In human preparations, however, I have not been able to demonstrate the *Rouget-cells*, even if I have frequently seen nuclei, bearing a remarkable resemblance to the *Rouget-nuclei*; neither I nor Dr. med. B. Vimtrup (who has most kindly examined some of these preparations) dare make any definite assertion on this point. In human preparations many different nuclei are found around and on the capillary wall, and many of these nuclei, stained with methylene-blue, present the same spotted appearance, the dye being precipitated in the nuclear substance. Even if many of these nuclei strikingly resemble the *Rouget-nuclei*, no certain conclusion can be drawn from this.

The nerves of the human capillaries, however, also form *one continuous, closed nerve-net*, and I have never seen free endings. In man, however, the nerves seem more frequently connected with the other nerves of the tissue than was the case in the animals examined — this may, however, be accidental. These connections are formed by thin, always non-medullated fibres; such fibres also connect the nerves of different capillaries, similarly as described in *p.* 67. In man the capillary nerves seem to contain still fewer nuclei than in guinea-pigs and rabbits; for long distances only the fusiform and varicose swellings in the course of the nerve are seen; these swellings I remarkably often saw as ring-like structures in human preparations, the centre being unstained; in other places, however, they were compactly stained.

Veins.

In man, too, the nerves of the small veins seem directly continuous with the nerves of the capillaries; in a few preparations (*hernial sacs*) I even

succeeded in substantiating a continuous nerve-net, which extended, without the slightest break, from a little artery, along some capillaries, being at last undoubtedly continuous with the nerve-net of a little vein.

For the rest the innervation of large as well as small veins was found to be fundamentally identical with the innervation of the veins of the guinea-pig and the rabbit.

SPECIAL PROBLEMS

Ganglion Cells on the Blood-Vessels.

Several times I have seen cells on the blood-vessels which, in my opinion, are nerve cells. In order that a certain cell may be considered as a ganglion cell

- 1) the cell must present a typical appearance, and
- 2) the cell must be continuous with unquestionable nerves.

If these criteria are dispensed with, as some investigators do, one is no longer on safe ground. Speaking here of ganglion cells, I exclude the cells of the large plexuses around the large visceral vessels (*carotis, renalis etc.*, also *vena cava inf.*); here, only cells on small peripheral vessels are in question, far from such places where the cell might be only part of larger nerve-plexuses without a distinct relation to the vessel. To determine whether a certain ganglion cell is of importance to the vessel on which it lies, it must be demanded, that the processes of the cell are directly continuous with the nerves of the vessel.

As will be seen in the physiological part of the present work, the possible existence of these particular cells has interested the physiologists very much, especially the question as to whether these ganglion cells would be able to take over the regulating function after the connection with the central nervous system and the sympathetic trunk is broken off.

I have seen such cells several times during the present work, but always *only on visceral arteries* and *only on precapillary arteries*, never on larger arteries and never on capillaries or small veins; the cells have been found in the guinea-pig, as well as the rabbit and in human preparations.

In all of the three organisms examined these cells in a remarkable degree presented the same appearance (*fig. 15*): On the precapillary artery, either just at the point of division or quite close to it, a globular, strongly stained cell, 4—8 μ in diameter, is seen lying *directly* on the vascular wall (the cells have been seen lying upon the vessel as well as in profile). The nucleus is large and vesicular, often provided with numerous granula, nearly always with a distinct nucleolus. Through 3—5 processes, which are stained exactly as the other nerves of the vessel, the cell is connected with these — or forms

these. The nerves are continued upon the vessel — and only upon the vessel — for so long as it is possible to follow them in the preparation.

That these cells are ganglion cells I am quite convinced; that they are of importance to the innervation of the vessels, I think extremely probable. The fact is that they are directly continuous with nerves which present exactly the same appearance and course as the only nerves found in vessels of this size: The reticular (sympathetic, motor) nerves.

That these cells should form the much disputed 2. sympathetic neuron I think improbable. The ganglion cells found must rather be considered as a peripherally displaced 1'. neuron, as it is seen elsewhere in the visceral system (the gastro-intestinal tract). A fundamental difference might then be supposed to exist between the innervation of visceral arteries and arteries of the extremities, the 1'. sympathetic neuron for the visceral arteries being displaced to the periphery, while for the arteries of the extremities — in which these cells were never found in spite of very painstaking examination — it should be placed in the sympathetic trunk.

It must, however, be stressed that the said ganglion cells are not so numerous, even in visceral arteries, that they might be supposed to form the whole of the 1'. neuron. I think it more probable that *a few* of the sympathetic tracts to the visceral vessels are not interrupted in the sympathetic trunk, and that the 1'. neurons of these tracts are placed peripherally (*i. e.* on the vascular wall), while this neuron usually lies either in the truncus sympathicus or in the large visceral nerve-plexuses, the demonstrated condition being rather the exception than the rule.

Connections between Reticular Nerves and Nerves Having Free Endings.

As mentioned in the historical introduction, it has been asserted by several previous investigators, most strongly perhaps by *Ioris*, that the sensory and motor nerves of the vascular wall form joint plexuses around the vessels (*Ioris's "plexus mixte, sensitivo-moteur"*).

As will be evident from the previous pages of the present work, I have not been able to confirm this assertion. As to the larger vessels this might be due to the circumstance that the whole of the surroundings of the vessels could not be examined in the preparations, and as to the lesser vessels it might be supposed that the demonstrated plexuses really were "mixed", the nerves having free endings being merely not stained.

The last objection can, I think, be dismissed at once. Even if this might be the case with some, perhaps, many of the preparations, it should seem almost certain that the facts would be revealed even though only in *one* preparation, from *one* of the animals examined; the here propounded view is moreover supported by degeneration-experiments (see part II).

In the larger vessels, however, nerves having free endings *were* seen, while the examination of the periarterial tissue in the same preparation as the vessel itself had to be given up. With this question in view the *femoral arteries* of some *mice* were examined, the whole of the periarterial tissue (and more) being present in the same preparation: By this procedure also, no hint was found of joint plexuses in even one single preparation; on the other hand, I frequently saw nerve trunks proceeding to the vessels, here dividing into branches, of which some, most frequently non-medullated, went to the nerve-nets, others, mostly medullated, ended in free terminations in the adventitia.

Finally the actual facts might often be studied in medium-sized arteries from guinea-pig as well as rabbit and man. There can be no doubt that the nerves of the two kinds of nerves often run to the vessel in the same trunks; but in the periarterial tissue, sometimes even at a considerable distance from the vessel, the trunks divide and the nerves are distributed according to their nature, *without* forming common plexuses; that relations in some preparations may be difficult, in others impossible to disentangle, is another matter.

The only connections which take place in and around the vessels between the reticular nerves and those having free endings, are formed by the above described coarse, non-medullated fibres, provided with large nuclei of *Remak*, which are frequently seen crossing from the afferent nerves of the nerve-nets (*never* from the nets themselves) to larger trunks of the nerves having free endings.

My findings do not confirm *Ioris's* "*plexus mixte*" — nor is a "ganglionnaire" plexus to be found, as will be evident from the above.

Nor am I able to confirm *Woollard's* finding of a sensory nerve-trunk, winding spirally round the vessels for long distances, and receiving segmental reinforcements in its course — *i. e.* a sort of sensory plexus; how this illusion may be produced will, in my opinion, be evident from *fig. 12*, in which a nerve-trunk starts winding round the vessel, without, however, forming the least connection with the other nerves of the vessel, which, on the contrary, end in free terminations independently of the new nerve. As I have found it, the freely terminating nerves of the blood-vessels are without other connections with other nerves or with each other than that formed by the above-mentioned single, non-medullated fibres, and I have never seen any indication of plexus-formation in their course. Nearly always dividing dichotomously they end freely, like the branches of a tree.

Ultimate Relations between Muscle and Nerve.

As will be evident from the historical introduction, very early, some investigators thought they had found intracellular, nay, even intranuclear

nerve-endings in smooth muscle, also in that of the blood-vessels; simultaneously, however, other authors thought they had found the ultimate nerve-endings of the muscularis as a network of thin fibrils — a *true terminal nerve-net*. That not everything described as "terminal nets" was so, is quite certain; just as certain it seems to me, that much of what was called "free, knob-formed nerve-endings" can only have been incomplete staining of the nerve-net.

On the basis of the present work alone it is not possible to take up any definite position in this question, which is one of the most interesting in neuro-histology; in this work it is not so much the ultimate endings of the nerves as their arrangement within the vascular wall which has been the object of study; this question cannot, however, be entirely disregarded.

As will be evident from what has been previously stated, one group of the vascular nerves was in this work found to end in a *closed, continuous nerve-net of thin neuro-fibrils* — seemingly a true, anatomical network (*rete*); with complete staining I have never seen free nerve-endings in the muscularis of the blood-vessels, — as *Michailow* found in his *first* preparations and as *Woollard* still asserts. On the other hand, I — *especially in the beginning* — obtained incomplete staining of the nerve-nets, and in these places the most beautiful "free, knob-like nerve-endings" are to be seen. In other places, also in fully stained preparations, one for a moment seems to see a knob-like ending — but a slight turn of the micrometer-screw reveals the fibre continuing, only in another plane.

With *Fukutake* and *Michailow* and numerous other investigators I suppose, judging from what I have been able to see, that the sympathetic nerves in the muscularis of the blood-vessels *end in a terminal nerve-net of thin neuro-fibrils*, which supposition also agrees very well with certain physiological facts, and that the "free, knob-like nerve-endings" in the muscularis of the blood-vessels are *artefacta*, but I dare not definitely deny the existence of free nerve-endings in smooth muscle, be it extra- or intra-cellular, because I have not been able to see them, while I can quite subscribe to *Ioris's* fine words:

"Ce n'est pas en vain que j'ai connu les travaux de mes devanciers; un enseignement, que je ne veux pas négligé se dégage de leur étude. Le plexus intramusculaire représente la mode de terminaison des fibres motrices jusqu'au moment où furent découvertes les fibrilles boutonnées qui en émergent. Celles-ci sont considérées comme terminales, parce qu'on ne soupçonnait pas l'existence des neuro-fibrilles qui les prolongent.

Pourquoi m'exposer à mon tour aux mêmes causes d'erreur en affirmant que les réseaux neuro-fibrillaires sont terminaux, parce que dans mes préparations il paraît être ainsi?"

SUMMARY OF ANATOMICAL PART

From the preceding pages it will be evident:

1. That the peripheral innervation of the blood-vessels examined with the technic employed exhibits no fundamental histologically recognisable difference in the animals examined;
 2. that the blood-vessels of the animals examined are in the whole of their course provided with nerves;
 3. that these nerves may be divided, morphologically, into two groups:
 - a) *Nerves having free endings*, which are most frequently *medullated* to their terminations, which are to be found on larger vessels only and only in the outer layers of the vascular wall (*adventitia*), while they are never found in the deeper layers; these nerves have been observed in connection with unquestionably sensory structures. Similar nerves are frequently found in intimate relation to smaller vessels, even the capillaries;
 - b) nerves, which are *always non-medullated*, whose arrangement in the walls of the blood-vessels is characterised by the formation of *peripheral nerve-nets* and whose finest ramifications seem to *end in a closed net of neuro-fibrils*, which is probably placed *extracellularly* between the individual muscle-cells, touching these opposite their nuclei;
 4. that nowhere in the described nerve-nets was it possible to find any indication of a separation in segments or zones which might be neurogenically distinct, but that the peripheral nerve-nets of the vascular wall may be imagined as *one continuous nerve-net throughout the whole of the vascular system*;
 5. that the histological substratum for an innervation of the *Rouget-cells* of the capillaries is present, nerves having been observed touching these cells opposite their nuclei;
 6. that peripheral typically sympathetic ganglion cells have been found on certain small vessels (*precapillary arteries*) of the *visceral* system, while no such cells have ever been found on vessels from the extremities, neither small nor large.
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II.

PHYSIOLOGICAL STUDIES ON THE NERVES
OF THE BLOOD-VESSELS

*„Les connaissances anatomiques forment
sans aucune doute une base indispensable,
mais la solution d'un problème physiologique
ne peut jamais arriver par cette voie-seule“.*

Claude Bernard.

ORIENTATION

The rational physiological investigation of the innervation of the blood-vessels is of comparatively recent date, as it may be said only to have started with the pioneer-work of *Claude Bernard* about the middle of the previous century.

Earlier still, however, attempts were made to form an opinion of the influence of the nerves on the blood-vessels. Thus *Senac* (1749) thought, that the arteries accelerated the blood-stream through rhythmical contractions, these being brought about by a "*succus nervus*", which was secreted from the nerves, and which acted as an astringent on the vascular wall. Curiously enough this theory — even though somewhat modified — has been revived in modern times, *Lewis's* theory of vasodilatation being based on similar principles.

Another, still older, theory has suffered a less fortunate fate — the theory which *Willis* (1685) hinted at and which was embraced by *Haller* a century later; *Haller* discovered by dissections that the nerves around the vessels were frequently arranged in slings and loops, and assuming that the nerves were contractable, he supposed that this nerve-plexus, by contracting and subsequently relaxing might directly open and close the blood-vessels: "*Nervorum in arterias imperium imprimis pendere autumamus a laqueis nervorum bifidorum, per quos mediæ arteriæ transeunt. Eos enim laqueos adstringi posse, incitato nervorum motu, minime dubium videtur. In cadavere quidem laxæ sunt & spatiosæ eæ ansæ & aliqua telæ cellulossæ vis arterias a nervulis separat. Sed in vivo homine plena sunt omnia & viciniora, & nullo modo fieri potest, si vel paulo strictior fiat nervus, quin sanguinis per arteriam motus mutetur*". Later on *Haller*, however, dropped this theory, *i. a.* because the pulse did not change even during the most violent convulsions in hysterical women (!), but his discovery of nerve-loops on the blood-vessels has been retained, though in a different garb.

Of physiological experiments on the innervation of the blood-vessels before the time of *Claude Bernard* I only think it necessary to mention a few, especially that of *Pourfour du Petit* (1727) ("*Mémoire dans lequel il est démontré que les nerfs intercostaux fournissent des rameaux qui portent des esprits dans les yeux*") ; *du Petit* had a dispute with the anatomists *Willis* and *Vieussenius* as to whether the nerves in the sympathetic trunk ran cranio-

caudally or conversely, *du Petit* maintained the last-mentioned theory; to support his views he cut the sympathetic trunk in the neck and, besides the well-known ocular symptoms, he observed a marked congestion of the conjunctiva.

Volkmann (1844) asserted that "*der Sympathicus ist die Grundbedingung aller selbstständigen Bewegungen der Eingeweide*" and the same year *Bidder* demonstrated that the circulation in the web of the frog might be maintained even if the brain and spinal cord were destroyed, thus proving the independence of the sympathetic system.

A really solid physiological basis for the innervation of the blood-vessels was, however, only reached by the investigations begun in 1852 by *Claude Bernard* and carried on by him in a series of experiments, which are some of the most clearly conceived and best executed experiments in the history of science. Not only did *Claude Bernard* contribute several new discoveries by his investigations, but he studied the vascular innervation so thoroughly and closely that later investigators have only been able to add or take away very little.

Even if besides *du Petit*, *Dupuy* and *Brachet* also had furnished some observations, it was unquestionably *Claude Bernard* who laid a solid foundation for the supposition of vasoconstrictor centres for the blood-vessels in the truncus sympathicus, and he was the first who demonstrated that, among the symptoms following the section of the sympathicus, the *changes of temperature* take a prominent place; *Claude Bernard* himself thought that the elevation of temperature which he observed after section of this nerve, was primary in relation to the vasodilatation.

In 1858 *Claude Bernard* discovered that by irritation of the *chorda tympani* he got not only a marked secretion of saliva from the submaxillary gland, but in addition a violent vasodilatation of the vessels of the gland; through atropine he was able to suppress the secretion of saliva, while the vasodilatation was unchanged, and he therefore thought it necessary in addition to the vasoconstrictor nerves to assume the existence of separate vasodilator nerves, and it was only then that all the factors were at hand, by which physiologists have subsequently attempted to explain the circulatory variations of the organism.

The Vasoconstrictor Nerves.

Claude Bernard studied the vasoconstrictor nerves after stimulation as well as after section. He stimulated the sympathetic in the neck of rabbits and observed vascular contraction and a fall of temperature in the corresponding ear; after section of the same nerve he observed a marked vasodilatation and elevation of temperature. These experiments showed 10: that vasoconstrictor nerves for the blood-vessels run in the sympathetic of the neck and 20: that these nerves possess tone.

These experiments and the conclusions which *Claude Bernard* drew therefrom were confirmed by a great number of investigators, only a few of which shall be mentioned *e. g.* *van der Becke Callenfels* and *Waller* 1855; *Buffalini* 1876; *Morat*, *Piotrowski* and *Langley* in the nineties; shortly after their appearance these conclusions were attacked by *Brown-Sequard*, but no importance was attached to his objections.

As to the vascular innervation of the extremities, it had been shown by *Wharton Jones* in 1851 that section of the sciatic nerve was followed by vasodilatation in the area of innervation and *Claude Bernard* as well as numerous other investigators (*Eulenburg & Landois*, *Saviotti*, *Ostroumow* in the seventies, later *i. a.* *Lewatschkoff*, *Lapinski*, *Nothnagel*, *Bernhardt*) confirmed this observation.

At this time these facts were generally understood to mean that the vasoconstrictor nerves for the legs run to the periphery in the sciatic nerve.

Several other investigators occupied themselves with *the central course of the vasomotor nerves*, into which I shall not enter in this place (*i. a.* *Pflüger*, *Jegorow*, *Langley*, *Gaskell*). On the basis of the experiments of these and several other workers a certain agreement as to the existence and course of the vasoconstrictor nerves has been arrived at and this belongs to the most cultivated fields of physiology; consequently I may omit details in this place and shall merely remind the reader that the existence of superior centres in the *brain* and *mid-brain* is supposed, and that the fibres pass to the *nucleus sympathicus lateralis* in the posterior horn of the *spinal cord*; from there they pass through the anterior root-bundles and the *rami communicantes albi* to the ganglia of the *truncus sympathicus*, where the nerves for the extremities are interrupted, and a new neuron continues through the *rami communicantes grisei* to the periphery. The sympathetic centres for the visceral organs, on the other hand, are supposed to lie in the innervated organs themselves. As to the course to the periphery there has been great dissension (*see p. 102*). Even in our day it has been supposed that the vasoconstrictor nerves might persist after the connection with the sympathetic trunk had been severed, and the existence of *peripheral centres* ("of *III order*") has been assumed. This question, however, will be treated later on.

Despite the above-mentioned dissensions the relations of the vasoconstrictor nerves may be said to be reasonably elucidated, at all events as compared with

The Vasodilator Nerves,

and for that reason I shall deal more fully with this subject. The term "*vasodilator nerves*" was introduced by *Claude Bernard*, whose well-known experiment on the submaxillary gland was mentioned above. His experiments were repeated and supplemented by several investigators, *e. g.* by *Eckard* in 1863,

who by stimulation of the *nn. erigentes* observed dilatation of the vessels of the *penis*.

On the other hand it took some time before dilator nerves were demonstrated for the extremities; it was not until the seventies that *Goltz* and his pupils supposed they could furnish the proof through their well-known experiments: If *Goltz* stimulated the newly cut sciatic nerve electrically, he obtained vascular contraction and a fall of temperature in the corresponding leg (*Goltz* worked on dogs), but 2—3 days after the section the same stimulation resulted in a marked dilatation. *Goltz* concluded that vasodilator nerves run in the sciatic, and that these nerves degenerate more slowly than the constrictor nerves, whose action masks that of the dilators in the freshly cut nerve. Finally it was found that also in the freshly cut nerve was it possible to demonstrate the dilators — *viz.* by stimulation with weak and less frequent electrical currents.

In 1855 *Schiff* showed that section of the large auricular nerve to the ear of the rabbit executed 10 days after the resection of the sympathetic in the neck, was followed by a dilatation of the blood-vessels of the ear.

In 1866 *Lovén* observed the reflex later named after him: If the central end of the cut large auricular nerve to the rabbit's ear was stimulated, a dilatation of the vessels of the ear followed. By stimulation of the *n. dorsalis pedis* *Lovén* obtained dilatation of the *vena saphena* and the *Lovén-reflex* (*i. e. stimulation of the central end of a cut sensory nerve results in vasodilatation in the adjacent area*) seems thus equally to hold good for veins.

Further work in this field has been furnished by *Gaskell*, *Frey*, *Bernstein*, *Huizinga*, *Kendall & Luchsinger*, *Latschenberger & Deahna*, *Moreau*, *Putzeys & Tarchanoff*, *Riegel*, *Kowalewsky*, *Mathieu-Gley*, *Winkler* a. m. o., but to enter into detail would take us too far. It shall, however, be pointed out that, while many of these investigators accept the existence of vasodilator nerves, their statements as to the mode of action and the nature of these nerves are very obscure. Thus *Auerbach* and *Exner* think that these nerves innervate the longitudinal muscles of the vessels, whose contraction should result in a dilatation of the vessels, while *Ostroumow* thought that the dilators acted by restraining the tone of the constrictors; the same train of thought is the basis of *Gaskell's* "*inhibitory nerves*", as this investigator terms the dilator nerves.

As to the *nature* of these nerves opinions differ; *Dastre & Morat* think that they are of a sympathetic nature, but the proofs of these authors for the existence of sympathetic dilators seem unconvincing; by stimulation of the sympathetic in the neck they obtained vascular contraction in various places, but a pronounced dilatation in the oral mucous membrane, and by other experiments they thought they could prove that this dilatation was caused by sympathetic dilator nerves.

The generally accepted view, however, seems to be that of *Ostroumow*,

according to whom the dilators act as "*inhibitory nerves*" on the tone of the constrictors. *Lapinski*, who worked at this subject in 1926, goes further still; he quite denies the existence of vasodilator nerves ("*das Spiel der Gefäße — — — kann man sich nämlich ganz gut logisch mit dem Hemmungsvorgang in den Vasoconstrictoren erklären*") ; if *Lapinski* stimulated the sympathicus in the neck with weak currents, he got vascular contraction ; if, however, he continued the stimulation for a long time, or if he at once used a very strong current, the result was a vasodilatation. These facts he explains by assuming that in the first instance he stimulated, in the last instance paralysed the constrictor centres of the sympathicus.

Furthermore *Lapinski* repeated the experiments of *Goltz* ; he stimulated the peripheral end of the cut sciatic 1—4 days after section ; either he obtained no effect at all or the result was a vasoconstriction. If, on the other hand, he stimulated the central end of the cut nerve, he — as above — got : with weak currents a vasoconstriction, with strong currents a vasodilatation, and in his opinion this is explained as respectively stimulation and overwhelming of the vasoconstrictor centres ; in the vasodilatation in the last-mentioned experiment the elevation of blood-pressure which occurs, was supposed to take a part.

A totally different explanation has arisen out of the observations of *Stricker*. In 1876 *Stricker* discovered that stimulation of the posterior roots of the spinal nerves is followed by a vasodilatation in the innervated areas. This observation was confirmed by *Bayliss* (1900), and this worker supposed that the nerves in question had their trophic centres in the spinal ganglia, and that they were identical with ordinary sensory nerves. In order to explain how these nerves — contrary to the general opinion — might transmit centrifugal impulses, *Bayliss* introduced the idea of "*antidromic impulses*". *Bayliss* moreover thought that the action of these nerves can *not* be compared with the action of the constrictor nerves, but he thought that the immediate effect of the antidromic impulse might be the liberation of a vasodilator substance in the nerve-endings. This idea was also mentioned by *Langley* and *Gaskell*.

It is, however, *Lewis* who in recent times has formed and laid the foundation of this theory of vasodilatation. *Lewis* pointed out that if he stimulated the sensory nerves of a cutaneous area whose sympathetic innervation had previously been destroyed (extirpation of the ganglia) after a noticeably long latent period (20—40 seconds) he saw a vasodilatation, which only vanished after 5—10 minutes ; he pointed out, moreover, that the vasodilatation was approximately proportional to the duration of the stimulation, when this time was not very long. In addition *Lewis & Marvin* found that the duration of this vasodilatation depended on the circulation of the area in question, only disappearing a certain time (5—10 minutes) after the restoration of circulation, this having been arrested during the experiment.

These relations he found for the vasodilatation of the *skin*, while he was unable to find them in the case of the *nn. erigentes*, and the mechanism of vasodilatation of these nerves must consequently be otherwise explained. *Lewis* concludes: "*These observations are compatible with one interpretation only, namely, that the antidromic impulse liberates a vasodilator substance in the skin during circulatory arrest, that it is held there until the release, and that it is then gradually removed. We conclude that the antidromic nerve-impulse influences metabolism in the cells of the skin, releasing in the tissue-spaces a vasodilator substance, and we have in mind especially the epidermis, which, as Ranvier has shown, is plentifully and intimately supplied by nerve-fibrils belonging to the sensory nerve-system*".

The substance secreted in the nerve-endings *Lewis* terms "*H-substance*", and he seems to consider it identical with *histamine*.

On the basis of these experiments *Lewis* thinks that *Doi's* and *Krogh, Harrop & Rehberg's* supposition of vasodilator nerves to the capillaries is untenable, as these vessels should react directly to "*H-substance*"*). It may, however, be doubted whether this holds good; even if all vasodilatation takes place through antidromic impulses, it might very well be supposed that the vessels possessed sensory nerves of their own, independently of the cutaneous nerves. *Lewis's* theory seems very plausible at the first glance, but it must be remembered that the antidromic impulse is as yet only known from experiments — *i. e.* from most "unnatural" conditions, and it must still be doubted whether "antidromic impulses" take so prominent a part in the vascular reactions of the organism.

As will appear from the above, great differences of opinion exist as to the vasodilator nerves: Some (*Higier, Ebbecke, Lewis* and his pupils) think that the ordinary sensory nerves are the anatomical substratum of these nerves; others (*Dastre-Morat*) think that they are of a sympathetic nature, and still others (*Lapinski*) are of opinion that these nerves do not exist at all; some (*Auerbach, Exner*) have thought that the action of the dilator nerves was to incite the longitudinal muscles of the blood-vessels; others (*Ostroumow a. o.*) think that they depress the tone of the constrictor nerves and still others (*Langley, Lewis*) consider it probable that they secrete a vasodilator substance.

The Physiological Aspect of the Problem Muscle-Nerve.

While thus some investigators seem to assume that no direct relation exists between the muscles of the blood-vessels and the vasodilator nerves, these nerves influencing the muscles *indirectly* by secreting a vasodilator

*) *Harris* found in 1927 that histamine is present in the skin in an amount of about 10 mgr. per/kg. tissue; histamine was also found in intestines, liver etc.

substance, it would seem more probable that the relation of the constrictor nerves and vascular muscle was of a more intimate nature. As to the *anatomical aspect* of this question *see p. 87*.

While the short latent period and certain other circumstances indicate a rather intimate relation between the constrictor nerves and the muscles of the vessels, other observations seem to indicate that this relation is in no way to be compared with the motor innervation of *striped* muscle. If the trophic centre of a striped muscle is destroyed, or if the connection between the two is severed, the muscle atrophies; it might therefore be interesting in this connection to study how the muscles of the vessels behave after degeneration of their nerve-supply. As a matter of fact some observations of this kind are to be found in the literature:

When *Goujon* (1867) thinks that two times out of three he has observed cerebrospinal meningitis after section of the sympathetic in the neck he has surely been deceived by the consequent vascular dilatation.

Giovanni (1885) has observed scattered atheromatous degeneration of the wall of the aorta some months after section of the dorsal sympathetic; he thinks that the sympathetic vasomotor nerves are of trophical significance for the vascular muscle.

In 1895 *Bervoet* saw degeneration of the vascular walls with aneurysmatic formations, obliteration of the lumina and proliferation of the intima some months subsequent to section of the sciatic in rabbits.

In the following year *Fraenkel* found a marked thickening of the walls in arteries, and especially in veins, some months after section of the sciatic in dogs; the lumina of the vessels did not seem markedly narrowed.

Czyblarz & Helbing (1897) performed the same experiment in rabbits and observed proliferation of the intima and thickening of the media in *some* of the animals. These changes, however, were only found in those animals which had had *trophic ulcers*, and the two investigators thought that the changes in the vessels were secondary to the ulcers — while the opposite might just as well be supposed.

The most exhaustive work on this problem, however, has been done by *Lapinski*, who in 1900 examined the vessels of rabbits in which he had removed part of the sympathetic in the neck; all of the animals exhibited the symptoms usual after this operation, the symptoms continuing until the animals were killed. 10—36 days after the operation the only pathological discovery was a slight thickening of the endothelial layer of the intima in the small vessels. 7—10 weeks after the operations the *larger* vessels in the denervated area showed thickening of the media as well as the elastica, the *smaller* vessels exhibiting the histological picture of an *endarteriitis obliterans*; the adventitia, too, was thickened, the intima had proliferated, the

lumen was in some instances quite obliterated, while the muscle had quite disappeared in some places and was everywhere quite thin.

The direct cause of these changes *Lapinski* seeks in intra-vascular mechanical conditions (dilatation, changes in the rapidity of the blood-stream, changed intra-vascular pressure), but it is due to the trophic influence of the vascular nerves that these factors do not harm the vessels in the normal organism.

In 1903, however, *Floresco* repeated these experiments, but was unable to observe the changes described by *Lapinski*; *Floresco* saw neither thickening of the vascular wall nor obliteration of the vessels — the only pathological changes he observed were some perivascular plasma-cells.

Certainly it also deserves to be pointed out that the diagnosis of *endarteritis obliterans* is frequently very difficult as soon as the plane of section is not exactly at right angles to the axis of the vessel, and the pictures of *Lapinski* do not seem quite convincing in this respect.

Finally it may be added that *Brandsburg* (1925) records degeneration of the muscle of the heart 4 months after extirpation of the sympathetic.

The histological observations enumerated do not, then, appear to furnish an answer to the question of the degeneration of denervated muscles of the vessels, and thus the literature does not aid us in elucidating the problem of muscle-nerve in the blood-vessels.

Physiologists have, however, again and again pointed out that denervated vessels may recover their tone; the initial dilatation subsequent to the extirpation of the sympathetic disappears, and the vessels behave like normal vessels; this is, however, especially stressed by workers who seek to prove the existence of *peripheral ganglion cells on the blood-vessels* ("*vasomotor centres of III order*") (*Goltz, Ostroumow, Gley, Asher, Leriche*), but in that case the vessels in question would not have been denervated at all.

As to this question I cannot help thinking that all physiological experiments for the elucidation of the problem might have been spared; *no safe conclusion can be drawn with regard to the degeneration of nerves except on the basis of histological investigations*: If the nerves disappear after extirpation of the corresponding parts of the sympathetic, these "*vasomotor centres of III order*" cannot exist, and all indirect reasoning from physiological experiments is futile.

That the vascular nerves degenerate after the connection with the sympathetic is severed was shown by the experiments of *Lapinski, Eugling* and *Woollard*. Whether, however, there may exist peripheral "*nerve-cells*" which take part in axon-reflexes *without being of trophic importance* is another question, but even then these cells will not be ganglion cells in the ordinary sense of the word; that several workers have taken the nuclei of *Remak* for such "*nerve-cells*" is mentioned in Part I.

It appears, however, that several investigators have observed sympathetic-

ectomised animals for a considerable time *without* noticing any disappearance of the paralytic effects on the muscles of the vessels. *Spalitta-Consiglio* observed an elevation of the temperature of the foot 13 months after extirpation of the lumbar sympathetic; *Jonnesco & Floresco* observed hyperemia of conjunctivae and gingivae in man 3½ years after a lesion of the sympathetic in the neck, while 5 years after the operation *Pye-Smith* saw unchanged maximal dilatation of the auricular vessels in a rabbit in which the sympathetic of the neck had been removed and the peripheral auricular nerves severed.

Langley, too, thinks that the paralytic symptoms do not disappear completely: "*The paralytic effects of section of the cervical sympathetic continue indefinitely, but they diminish in intensity*", but it would thus seem that the matter is not quite clear. We do not obtain a definite answer to the question of the behaviour of denervated, smooth muscle by experiments of this kind either; it may, however, be assumed that an atrophy corresponding to that of a striped muscle after section of its afferent nerve, does *not* appear in denervated smooth muscle.

If then the muscles of the blood-vessels are capable of retaining or regaining their tone, this "tone" cannot be of a nervous nature, but we must assume with *Langley*, "*that the most probable explanation of such recovery of tone as occurs, is the inherent contractable power of the plain muscular tissue itself*".

That denervated vascular muscle does not quite lose its power of reaction was already shown by *Elliott* in 1905 (hinted at by *Brodie & Dixon* in 1904); *Elliot* discovered that not only do all sympathetically innervated smooth muscles react to adrenaline by contracting, but even all muscles, which *have previously been* so innervated. *Elliot* concluded that adrenaline acts neither upon nerve nor upon muscle, but upon "*the myo-neural junction*", a point which cannot be of a nervous nature "*in so far as its trophic centre lies in the muscular nucleo-plasm*".

These facts were almost simultaneously confirmed by *Langley*; this worker, however, concludes from the reactions of the muscles to nicotine and curare that these substances as well as adrenaline "*do not act directly on the contractile substance, but on other substances in the muscle, which may be called receptive substance*", and he concludes: "*So we may suppose that in all cells two constituents at least are to be distinguished, a chief substance, which is concerned with the chief function of the cell as contraction or secretion, and a receptive substance, which is acted upon by chemical bodies and in certain cases by nervous stimuli*".

As it appeared from the anatomical introduction, *Boeke*, in his "*periterminal net*", claims to have discovered the anatomical substratum of this "receptive substance".

Hence physiologically also, no definite opinion can be formed as to the problem muscle-nerve in the case of the blood-vessels.

How Do the Nerves of the Blood-Vessels Reach the Periphery?

This question is of especial interest for periarterial sympathectomy, and I shall therefore enter more fully into the problem.

While the early opinion was that the vasomotor nerves ran in the ordinary, peripheral nerve-trunks, because after section of these trunks vascular dilatation and rise of temperature were noted in the corresponding areas, several investigators had, on the other hand, hinted that at any rate part of these nerves possibly ran in *long, perivascular tracts*.

Now J. Dogiel (1872) was unable to demonstrate any paralytic symptoms after section of the sciatic in frogs: Artificial wounds in both extremities apparently bled with equal profuseness whether or not the sciatic was cut. Dogiel therefore concluded that no very great part of the vasomotor nerves run in the sciatic nerve of the frog — even if this experiment in reality only showed that such nerves, if present, did not possess tone.

Dogiel's conclusions were, however, supported by Humilewski, who arrived at the same opinion, though in a different way. Contrary to Dogiel he saw vascular constriction in the web of the frog after stimulating the corresponding sciatic, *but he furthermore found* that no contraction took place when he had given the animal curare. In dogs he, like previous investigators, found that stimulation of the peripheral stump of the cut sciatic or crural nerve resulted in a marked elevation of blood-pressure in the corresponding leg, *but he furthermore found* that this elevation was almost proportional to the simultaneous contraction of striped muscles; the more centrally he stimulated, the greater the elevation. When now he gave the animal curare and repeated the experiment, he saw *no effect on the blood-pressure*; he therefore concluded that the elevation of blood-pressure was not — as previously supposed — due to vascular contraction following stimulation of constrictor nerves in the sciatic, but was only an accompanying phenomenon of the contraction of striped muscle, and he concludes: "*Somit kann die Anwesenheit von vaso-motorischen Nerven im Ischiadicus oder im Cruralnerven eher bezweifelt als angenommen werden*".

The results of Humilewski were supplemented in 1892 by the experiments of Jegorow. This worker found that (electrical) stimulation of the peripheral as well as the central end of the sciatic in frogs had no effect whatever on the circulation of the web, nor were any changes brought about by stimulation of the spinal nerves. Only by stimulation of *the sympathetic trunk* itself did Jegorow observe strongly marked contraction of the vessels, and he found some effect by stimulation of the *sacral plexus*; this effect,

however, disappeared after complete isolation from the sympathetic. Finally *Jegorow* stimulated the sympathetic trunk after having previously cut the sciatic, and even then the result was a marked vascular contraction in the web. He concludes that the vasomotor nerves run *perivascularly* from the sympathetic trunk to the blood-vessels of the web — even if these experiments in reality only showed that such nerves do not run in the sciatic.

The experiments of *Jegorow* convey the impression of having been very carefully executed, and it is strange that no later worker has been able to confirm his results. Now it must be conceded that experiments of this sort are difficult in frogs, the degree of reaction seemingly varying with the varying state of the individual frog — even if I, personally, have never seen variations in the nature of the reaction — anyway, all later works with frogs as well as with other animals have shown the diametrically opposite result: The vasomotor nerves of the legs run in the peripheral nerve-trunks and, after section of these, *no* vascular contraction is to be seen upon stimulation of the sympathetic.

Thus the experiments of *Langley* on cats (1923), as well as several experiments since the time of *Claude Bernard*, have produced identical results.

The conception of long, perivascular tracts, however, seems to die hard, and attempts have been made to demonstrate these hypothetical tracts also by *direct stimulation*. *Schilf* (1924) was, however, unable to get any contraction of the distal vessels of the leg after stimulation of the perivascular tissue around the femoral artery — he sometimes observed a doubtful, very slight *dilatation*, which, however, disappeared after section of the crural nerve.

On the other hand, *Leriche & Policard's* investigations in man seem to indicate the existence of long perivascular nerve-tracts; these workers observed contraction of the capillaries of the nail-fold during the operation of periarterial sympathectomy on the brachial artery.

Feldberg (1926), however, thinks that all the vasomotor nerves for the rabbit's ear run in the peripheral nerve-trunks.

Combined Anatomical and Physiological Investigations.

It might be thought that many of the numerous physiologists who have investigated the innervation of the blood-vessels would frequently feel tempted for once in a while to *see* these vascular nerves, of whose existence they only knew from their effects. Moreover, one can never be quite sure, even in very carefully executed degeneration-experiments, that no nerves remain intact until complete degeneration has been demonstrated histologically, and this argument is, as a matter of fact, met with again and again in the physiological literature on this subject.

Hence it seems curious that *combined anatomical and physiological*

experiments are not more frequently met with than is the case: I have only been able to find *three* investigations of this kind, in addition to the few experiments which *Langley* (1909) performed in frogs, without, however, combining them with physiological studies.

These three investigations were made by the Russian *Lapinski* (1905—06), the Germans *Hoffmann & Eugling* (1907—08), and finally the American *Woollard* (1926). In all three series the nerves were stained by means of *methylene blue* — rather unfortunately, partly because a verification series with impregnation would have afforded more security, partly because this method of staining — though it may give excellent results — frequently fails at the crucial moment, nobody being able to say why. I shall now enter more fully into these three investigations.

Lapinski used dogs for his purpose; anatomically he found the arrangement of nerves as mentioned at p. 29, and he now wished to determine whether these nerves took their course along the sciatic or along the femoral nerve; *Lapinski* did not, however, investigate the nature of these nerves — he took them all to be sympathetic; so he performed no ganglionectomies. Subsequent to section of the *femoral* nerve *Lapinski* thought he saw only some few, isolated nerves in the adventitia of the vessels disappear — all the other nervous elements were unchanged, and the animals exhibited no special symptoms.

Subsequent to *section of the sciatic nerve* on one side *Lapinski*, however, saw hyperemia and a rise of temperature in the corresponding leg; these phenomena disappeared in the course of some weeks. *Histologically* he already found demonstrable changes in the *medullated nerves* of the vessels *in the first week*: The axis-cylinder seemed, as it were, to divest itself of the medullary sheath which swelled and formed scattered lumps. The axis-cylinder itself exhibited vacuolar degeneration from *2 weeks* after the section of the nerve. *The non-medullated fibres* showed granular degeneration during the *2nd and 3rd week* and finally disappeared completely.

After some months no trace of nervous elements was discernible in the vascular walls — all seemed to have disappeared.

From the investigations of *Lapinski* it thus seems proved beyond doubt that all vasomotor nerves for the hind-paw of the dog run in the corresponding sciatic nerve, but the nature of these nerves is doubtful.

Shortly afterwards *Hoffmann & Eugling* worked at the problem, using frogs and rabbits.

The frogs were examined after staining of the nerves with methylene blue 15—60 days after the operations; these were partly section of one sciatic, and partly resection of the lumbo-sacral and ischio-coccygeal plexus. A short time after the operations vascular dilatation of the corresponding web was observed, but this phenomenon again disappeared, and from 10—20 days after the operations the webs of the two sides were not to be distinguished from each other.

Histologically they found the nerve-plexus of the vessels — previously seen in normal animals — to be intact in the non-operated leg, but this plexus had disappeared on the *aa. digitales propriae* and the arteries of the *dorsum pedis* in the operated leg, well-stained nerves being, however, present on cutaneous arteries of the *thigh* and on the *superior sartorial artery*. *Eugling* thinks that this latter fact is due to the nerves for these vessels going off superior to the point of nerve-section. Moreover he thinks that the nerves for some arteries run along the vessels, as the superior sartorial artery (which goes off in the pelvis), also after section of the said pelvic nerve-plexuses, always presented well-stained nerves, while the nerves of the *inferior sartorial artery*, which springs from the *a. femoralis profunda*, had invariably disappeared.

In *rats* *Eugling* was unable to obtain useful results, but he especially examined the *a. auricularis media* of the rabbit's ear, in some animals after section of the cervical sympathetic, in others after section of the large auricular nerve, in still others after an attempt to extirpate the superior cervical and the stellate ganglia. Immediately after all his operations *Eugling* found a *vascular dilatation in both ears*; this dilatation gradually decreased during the following weeks, in some cases the artery of the operated ear was even found to be of smaller calibre than that of the non-operated ear.

While *Eugling* was able to get contraction of *the whole* of the *a. auricularis media* in normal rabbits by stimulating a single point in the middle of its course with induced currents, he did not succeed in this later than 8—10 days after the extirpation of the superior cervical ganglion, even when using very strong currents; on the other hand, he obtained contraction of *half* of the artery in rabbits in which the sympathetic had been only *cut*; moreover the artery on the side on which the ganglion had been extirpated in *one* case seemed broader than that of the normal ear — otherwise, and in the rest of the animals, no changes were to be seen.

Histologically 8 rabbits were examined, from 20—130 days after the operations. On the *normal side* *Eugling* found the central and the peripheral part of the artery provided with a wide-meshed adventitial nerve-plexus running longitudinally, while the middle part of the vessel, from which part alone the said contraction could be induced, was in addition provided with several fibres running transversely, and the nerves in this locality were more plentifully provided with nuclei. On the *operated side* *Eugling* found rudiments of the adventitial plexus in the middle part of the vessel in 6 rabbits, otherwise all nerves had disappeared. If *Eugling* examined the artery as early as 20 days after the operation, he found small rudiments of nerves in connection with the nuclei; these latter always seemed quite uninfluenced by the operation.

In the *lateral arteries*, which *Eugling* examined in some cases, the nerves were always preserved, even if the large auricular nerve had been cut. *Eug-*

ling was not quite sure of the cause of this: The explanation might be that part of the nerves — as shown by *Langley* — reached the vessels of the ear in the *accessory nerve*, but, it might also be possible that the extirpation of the ganglia had been incomplete and, moreover, that part of the nerves might run *along the vessels*.

Eugling concludes that, as the vascular nerves degenerate after extirpation of the corresponding sympathetic ganglia (or after section of the connections to these, as in the frog), *peripheral ganglionic nerve-nets in the sense of Bethe cannot exist*.

Eugling mentions the work of *Lapinski*, which had appeared a short time before. *Eugling* did *not* see the nervous elements of the *muscularis* of the vessels, which *Lapinski* describes, — *he only observed nerves in the adventitia*, and he himself thinks this due to incomplete staining. Thus *Eugling* did *not* observe how the terminal nets of the *muscularis* behave after ganglionectomy; hence his experiments become less conclusive; he himself sees this clearly, and he mentions as a possibility, that the explanation of the discovery of *Brodie & Dixon* (that "denervated" [the degeneration was not histologically proved] muscles are still able to react to adrenaline) might be the persistence of such terminal nerve-nets — or perhaps of as yet unknown nervous elements. Consequently, the investigations of *Eugling* are not convincing.

This, however, is not true of the work of *Woollard* (1926) as far as it goes. As to the *anatomical details* see p. 37.

Woollard finds, in cats, that the pads in the first days after lumbar ganglionectomy as well as after *one* of the three periarterial sympathicectomies performed by him show swelling and are distinctly more red than on the opposite side; these symptoms continue for at most 2—3 days, after which the pads of the two feet behave quite similarly. All the nerves in the *muscularis* of the vessels of the hind legs disappear after extirpation of the corresponding sympathetic ganglia; on the other hand, some medullated and a few non-medullated nerves persist in the adventitia. These nerves *Woollard* takes to be *sensory* nerves which run in the sciatic, but he does not investigate the nature of these nerves further. These last-mentioned nerves frequently encircle the lesser vessels spirally, and *Woollard* thinks that this nerve-spiral receives segmental reinforcements — in other words he finds a *perivascular, sensory (?) nerve-plexus*. This finding I have been unable to confirm in the present work (p. 87). The innervation of the *capillaries* *Woollard* takes to be exclusively sympathetic.

As to the path which the vasomotor nerves follow to the periphery, *Woollard* thinks that the vessels are provided *in two ways* — *in part* perivascularly, *in part* segmentally along the peripheral nerve-trunks. In cats he performed periarterial sympathicectomy on the common and external iliac arteries, and 50 days after the operation the nerves had disappeared at the site of

operation and somewhat distally to this; but as he examined the vessels more and more distally, he saw more and more nerves and comparatively soon — in cats at about the point of division of the femoral artery in the profunda — the nerves were of quite normal appearance and number.

According to *Woollard* impulses may travel to the vessels perivascularly as well as along the peripheral nerves, while the trophic innervation for the vessels of the extremities cannot, at any rate, be exclusively perivascular.

As will appear, only *two* combined anatomical-physiological investigations have been made, when that of *Eugling* is excluded owing to incomplete histological examination; of these two series, one (*Lapinski's*) was executed exclusively on the hind-legs of dogs, the other (*Woollard's*) was mostly concerned with the hind-legs of cats.

Now *Krogh* (1924) supposes that the peripheral nerve-nets of the vessels might perhaps survive if only some few fibres (along the vessels *or* along the peripheral nerves) connect the vessels with the nervous centres, and for the elucidation of this question *Woollard's* work is of no interest.

Consequently it seemed to me advisable, in connection with the anatomical examinations in the present work, to carry out some experiments for the elucidation of this question — and it seemed to me to be of especial interest to repeat the experiments of *Eugling* on the rabbit's ear — so frequently used in physiological work — and to supplement them with more convincing investigations.

The Capillaries.

The innervation of the capillaries has in recent times been the object of much discussion. Some workers think that the nervous control of the capillaries is of prime importance, other workers assume that it is of little or no importance. Thus *Langley* declares in 1923: "*Je pense que les variations dans le diamètre des capillaires sont probablement dues aux variations dans l'équilibre des pressions extérieures et intérieures des capillaires, ainsi qu'à l'action des métabolites, plutôt qu'à une influence nerveuse directe*", while *Lapinski* asserts in 1926 that "*ihre*" (*i. e.* the capillaries') "*Weite hängt von Tonus des sie umgebenden Gewebes ab, aber in noch grösserem Masse von der Kontraktionsfähigkeit und Kaliberweite der Arterien, die den Capillaren das Blut zuführen*".

For the anatomical substratum of an innervation of the capillaries see *Anatomical Part: Survey of Previous Work* and p. 60 & 67 & 75 & 83.

The nature of the nerves of the capillaries has been obscure until recent times. In 1920 *Hooker*, however, saw stimulation of the sympathetic in the neck produce capillary contraction in the corresponding rabbit's ear, and this fact has been confirmed by *Krogh* *a. o.* In the frog *Krogh, Harrop & Rehberg* (1922) demonstrated that the capillaries of the web contract after

stimulation of the 8'—10' sympathetic ganglia on the same side, and proved in addition that the capillaries of the web as well as of the rabbit's ear are subjected to a *vasoconstrictor sympathetic tone*, as these vessels promptly dilate subsequent to ganglionectomy, respectively section of the cervical sympathetic. The capillaries of the rabbit's ear seemed to regain their tone 1—2 days after the operation, while the capillaries of the frog's web were still dilated 100 days after ganglionectomy, only curiously fitful, temporary contractions being observed.

How the capillaries are able to contract seems comprehensible after *Vimtrup's* confirmation (1920) of *Rouget's* forgotten observation of contractile cells upon the capillary wall. After the discovery of these cells in warm-blooded animals (*Zimmermann, Gurwitsch*) and in man (*Schaly*), it seems permissible to adopt the view that these cells are not only — as some workers, *e. g.* in recent times *Ebbecke*, suppose — to be found in some few places in certain animals, but that they are a regular feature in the most different organs in the most different animals. After the work of *Zimmermann* and especially after that of *Bensley & Vimtrup*, these structures may reasonably be compared with smooth muscle-cells.

Nor does it seem quite evident *why* these cells should be restricted to some few animals and some few organs; no cause for such an assumption can presumably be found — beyond the single fact that these cells have not as yet been found everywhere, but this may easily be ascribed to technical difficulties. On the contrary, so long as it is not safely substantiated that these structures are peculiar to certain organs and why, it seems to me more reasonable to surmise that these cells form a regular part of the capillary wall.

Consequently the hypothesis of *Krogh* (1924) seems the most probable solution of the mechanism of capillary contraction: "*There is reason to believe, that every single Rouget cell is supplied from a sympathetic fibre and can be made to contract through it*".

The histological basis for this hypothesis is supplied in the first part of the present work (*p.* 68).

That *Lapinski* was wrong in asserting that the blood-stream is the important factor for the changes of calibre of the capillaries has been proved by *Krogh*. Moreover *Steinach & Kahn* (1903) (*membrana nictitans* of the frog), and later *Harris & Marvin* (1927) (rabbit's ear) have shown that contraction of capillaries following stimulation of the sympathetic *also* takes place *after arrest of the circulation* — which must be pronounced a rather decisive proof that the sympathetic nerves of the capillaries may effect contraction independently of the blood-pressure in the afferent arterioles.

Krogh's experiments with weak mechanical and with chemical stimulation of arterioles and capillaries in the web and tongue of the frog seem to indicate the presence of *dilator nerves* either upon these vessels or in their

immediate vicinity. In the anatomical part of the present work it was demonstrated that *nerves having free endings*, which were supposed to be sensory nerves, were not present upon the smaller vessels, but were frequently found in their immediate vicinity; this, however, was not true of all capillaries. Consequently an effect of these nerves upon *some* capillaries cannot be excluded when the antidromic impulses of sensory nerves and *Lewis's* theory are duly considered.

Now it was shown by *Doi* in 1920, and by *Krogh, Harrop & Rehberg* in 1922, that a large number, *even though not all*, of the capillaries of the frog's web dilate upon stimulation of the posterior roots of the spinal nerves; on this point, too, the histological evidence seems to bear out the physiological observations.

On the other hand, *Krogh & Rehberg* were unable to cause capillary dilatation in the rabbit's ear by stimulation of the afferent, sensory nerves; in this *Feldberg* (1926), however, succeeded (*see p. 123*) some time after extirpation of the sympathetic in the neck; the antidromic dilatation consequently seems to hold good also for the vessels of the rabbit's ear.

Whether these antidromic impulses in sensory nerves can also explain *Krogh's* local reflex of dilatation in frogs is, however, an open question; the best explanation would seem to be the existence of a vasodilator nerve-net upon the capillaries, but no such thing has been found; later on I shall return to this problem.

THE AUTHOR'S OWN INVESTIGATIONS

TO WHAT PART OF THE NERVOUS SYSTEM DO THE NERVES OF THE BLOOD-VESSELS BELONG?

In the present work two morphologically separated groups of nerves were found upon the blood-vessels: The *nerves having free endings* and the *reticular nerves*. It then remained to determine whether these two groups of nerves belonged to the same or to different parts of the nervous system; to this end the following experiments were executed:

Frog.

In 5 frogs (3 *esculentae*, 2 *temporariae*) the lumbar sympathetic was extirpated on the right side for as long a distance as possible, using the technic introduced by *Krogh, Harrop & Rehberg*. This operation is rather difficult: 3 of the frogs died and were replaced by other animals. The operation is most easily executed by a longitudinal incision in the back, opposite the iliac crest; working upon the side of the columna, one reaches the anterior aspect of the same, and it is now possible (sometimes!) to get hold of the sympathetic by means of a little bent glass-rod; the trunk is followed proximally as high as possible and extirpated; the incision is closed by a few silk-sutures in the skin. Urethane anesthesia.

For the functional consequences of this operation see p. 124.

Frog I was killed 30 days after the operation. After staining of the nerves in both hind-legs by methylene blue (as recorded in p. 46) the relations previously described (p. 55) were noted in the normal leg. In the *operated leg* the cutaneous nerves of the leg and the foot were of normal appearance and number. The nerve-nets upon the vessels previously found in normal frogs and now on the sound side had, however, quite disappeared in this leg, and only in two places — upon the *art. dorsalis pedis* and upon a little artery of the web — were faintly stained fibres discovered, and in these places it was possible to recognise rudiments of the *interlamellar* nerve-net; for the recognition the well-stained and apparently quite unaltered nuclei of *Remak*, which usually lie at the angles of this net, were useful; in connection with some of these nuclei was discovered a little "tail", as it were, a faintly stained, curiously granulated nerve-fibre, which was always quite short; most of the structures taken for nuclei of *Remak* did not exhibit these

"tails". Upon *arterioles* and *capillaries* *no nerves at all* were to be seen; on the other hand, nerves having free endings and the cutaneous nerve-plexuses were frequently seen lying in the immediate vicinity of these vessels, in several places only at a distance of 20—30 μ , but these nerves were nowhere to be seen upon the vessels.

Frog II was killed 40 days, *frog III* 50 days, *frog IV* 60 days, and *frog V* 70 days after the operation. The relations found were quite identical with those of *frog I*, with the difference that in none of these frogs was there any intimation of the usual nerve-nets, these nets always presenting the normal appearance in the sound leg; none of the nuclei of *Remak* exhibited any "tails". In the last frogs no signs of regeneration were noted.

Rabbit.

In 5 albino rabbits (3 males, 2 females) the left cervical sympathetic was extirpated through a longitudinal incision in the neck. Ether anesthesia. Taught by the results of *Feldberg I* carried the incision downwards and backwards, and by blunt dissection it was now possible to follow the sympathetic distally, until the stellate ganglion was reached; this part of the operation is rather difficult — one works at considerable depths quite close to the great vessels. As the results showed I succeeded in removing the whole ganglion in all cases, but in one case a strong hemorrhage occurred, and the animal had to be killed (chloroform); it was replaced by another rabbit. In all the animals the incisions healed *per primam intentionem*.

For the *functional consequences* of this operation see p. 129.

Rabbit I was killed (chloroform) 30 days after the operation, and the nerves in both ears were stained by means of methylene blue.

The *histological examination* showed: *Left side*: The great nerves along the *a. auricularis media* stained well and showed nothing abnormal compared with those of the right side. Upon the vessels themselves well-stained nerves were seen, these, however, for the most part being medullated and invariably found in the adventitia of the vessels only, where they ended in the free endings described in p. 73. These nerves were in several places seen to encircle the smaller arteries, but they did *not* end upon these vessels though frequently in their immediate neighbourhood; this, too, was the case with arterioles and capillaries; in one place a medullated nerve encircled a small vessel (capillary?) spirally, thereupon ending freely in the tissue, separated 30—40 μ from the vessel. This is the only place in which I have found nerves *upon* the smaller vessels after ganglionectomy. Nowhere was there any hint of the usual nerve-nets found in normal rabbits and in the non-operated side; a number of *nuclei* were noted, some very similar to nuclei of *Remak*, but even by means of these I did not succeed in discovering even as much as a trace of the usual nerve-nets, either in the adventitia or in the muscularis.

The *right side* exhibited normal relations (*see p. 71*).

Rabbit II was killed 50 days after the operation, and the nerves of the blood-vessels of both ears exhibited the same relations as described under rabbit I.

Rabbit III had the same typical, post-operative course as the other animals, but I did not in this case succeed in obtaining good nerve-staining on the non-operated side either — the staining was good only in spots; as this was also the case with other vessels from the same animal (*carotides, femorales*) I had to note that from unknown causes the staining had failed.

Rabbit IV and *rabbit V*, however, exhibited identical findings with rabbit I, respectively 38 and 43 days after the operation, and the nerve-nets in the non-operated ears were well-stained in these animals.

In none of the animals was any sign of regeneration noticed.

From these experiments I conclude that *the previously described nerve-nets of the blood-vessels in frogs and rabbits degenerate in the hind-leg of the frog and in the rabbit's ear after extirpation of respectively the distal part of the sympathetic on the same side and the cervical sympathetic on the same side. These nerves are consequently of a sympathetic nature and have their trophic centres in the removed part of the sympathetic or central to this. This cannot be true of the freely ending nerves of the blood-vessels.*

HOW DO THE NERVES OF THE BLOOD-VESSELS REACH THE PERIPHERY?

As mentioned in the introduction, conflicting opinions have existed as to the path which the vascular nerves follow to the vessels, and it was found, that new investigations in connection with anatomical examination would be desirable in order to clear up this question.

It was also found in the present work that the vascular nerve-nets discovered, which later degeneration-experiments showed to be of a sympathetic nature, in all places where they were accessible to examination, were continuous throughout, without any separation in segments or zones which might be segmentally innervated. While it was beyond doubt that the *aorta* was provided with sympathetic fibres *direct* from the sympathetic trunk, and the possibility of a *perivascular innervation* could not consequently be denied, the nerve-nets were in several places found to be continuous with branches from peripheral nerves, these branches providing the nets in the way described. Thus — judging from the anatomical relations alone — the innervation might just as well take place *segmentally from the peripheral nerves*. Last but not least, the possibility must be mentioned that the innervation might normally take place *either way* — it being sufficient to

prevent total degeneration of the nerve-nets that one road were intact. This would so to say be a *natural measure of precaution* against the degeneration of these important nerves.

As these problems were deemed of the greatest importance for the understanding of periarterial sympathectomy, I performed the following experiments for the purpose of determining whether the trophic innervation of the nerve-nets of the blood-vessels takes place perivascularly, or along the peripheral nerves or, possibly, by both these roads.

Frog.

In 10 frogs (5 *esculentae*, 5 *temporariae*) the right sciatic nerve was resected. Urethane anesthesia. A piece, $1\frac{1}{2}$ —2 cm. in length, was excised; the stumps were ligated with fine silk and the incision closed by a single silk suture.

All of the frogs exhibited typical circulatory disturbances in the web, as previously described by Krogh, see p. 125. After their deaths no signs of nerve-regeneration were found in any of the frogs.

48 days after the operation one frog (*esculenta*) was killed and the nerves of both hind-legs stained by methylene blue.

Histologically the *medullated nerves* were found the seat of a curiously, granulated-vacuolar degeneration, the larger medullary trunks in several places being quite filled up with large lumps without visible structure, frequently strongly refracting, but nowhere did I succeed in staining a single axis cylinder; in other places globular, small vacuoles were to be seen. The *non-medullated nerves* of the vessels had in certain places quite disappeared, but in a few places — especially in the distal part of the crural artery — well-stained nuclei of Remak were seen, and between these in scattered places a net-like formation could be recognised; these fibres were pale, curiously “empty-looking” — it looked as if only a *thin sheath* were left, these sheaths in places showing a net-like arrangement. In the deeper parts of the vascular walls no trace of nerves was seen, and upon the precapillary arteries and the capillaries all nerves had disappeared.

The vessels in the *non-operated foot* exhibited normal relations.

63 days after the operation 2 frogs were killed (one *esculenta*, one *temporaria*). After staining by methylene blue the nerves were examined *histologically*:

The *medullated nerves* of the skin of the operated leg still exhibited the above-described granulated-vacuolar degeneration. The course of these nerves was still distinct, marked by the large, structureless masses, which nearly replaced the nerve. The nuclei of Schwann were unchanged, and stained well as the staining proceeded; in many places small, strongly

refracting granules were seen. *Upon the vessels* no trace of medullated nerves was to be found, but in a few places (crural artery) was seen a short fibre, resembling the picture described above, of medullated nerves in degeneration. In several places nuclei quite resembling the nuclei of *Remak* were stained, and a few of these showed a little "tail"-like process, but it was nowhere possible, even by means of these, to reconstruct any net-formation, and no non-medullated nerves were to be seen.

79 days after the operation another 2 frogs were killed (one *esculenta*, one *temporaria*), 94 days after another 2, and 110 days after the operation the last 3 frogs. In none of these frogs were normal nerves to be found in or upon any of the vessels examined.

From these experiments I conclude that the reticular, sympathetic nerves of the vessels of the hind-leg of the frog degenerate completely after section of the sciatic nerve on the same side and must consequently run in this nerve; the freely ending nerves of the vessels behave in the same way.

Rabbit.

In *p.* 114 it was shown that the sympathetic nerves for the blood-vessels of the rabbit's ear have their trophic centres in the cervical sympathetic on the same side. To determine what path these nerves follow to reach the vessels, the following experiments were executed:

4 albino rabbits (3 females, 1 male). Ether anesthesia. Resection of about 1 cm. of the left *n. auricularis magnus*; the incision was made about 1 cm. from the root of the ear, and the stumps were ligated with fine silk; the incision was lengthened to each side and *n. ventralis & dorsalis auris* were sectioned and ligated; lastly 1—2 small branches, reaching the ear along the inner, inferior border, were equally sectioned and ligated. The incisions healed in all of the animals *p. p. i.* One rabbit (female) was found dead in the cage after 7 days; I did not succeed in finding any *causa mortis*.

All of the operated rabbits exhibited the postoperative course usual after an extirpation of the cervical sympathetic — see *p.* 135; moreover total anesthesia of the whole of the ear was present during the whole of the experiment.

The first rabbit was killed (chloroform) 30 days after the operation. No signs of regeneration were found in the sectioned nerves. Excised tissue from both ears was examined *histologically* after staining by methylene blue, and the following was found: In the operated ear *the medullated nerves of the skin* were strongly changed, partly faintly stained, partly in granulated-vacuolar degeneration; the course of the nerves was clearly to be seen due to the well-stained nuclei of *Schwann*, the nerves themselves being filled with

lumps of structureless masses containing doubly refracting granula. Upon the blood-vessels, too, these structures, which were taken for medullated nerves in degeneration, were noted. On none of the arteries of the ear, including the base of the middle artery, was any trace of the usual nerve-nets to be seen — only now and then a structure was met with, which was taken for a nucleus of *Remak*, but nowhere was it possible to reconstruct any nerve-net. Neither in the small arteries, the veins, nor the capillaries did I succeed in finding nerves.

Upon the vessels of the *non-operated ear* I found nerves having free endings as well as reticular nerves of the usual appearance and in the usual number.

60 days after the operation the *second rabbit* was killed; clinically it had exhibited the same symptoms as the first one. By the *histological examination* of the nerves, the same relations were found as in the first rabbit upon the anterior lateral artery, the middle artery, and the small vessels, but on the *central part of the posterior lateral artery* a little spot was seen in which the reticular nerves were of quite normal appearance; this place was the most central part of the vessels from the point of section and $\frac{1}{2}$ cm. peripherally; *the reticular nerves seemed quite normal here*; no nerves having free endings were seen. The transition between that part of the vessel which had preserved its nerve-supply and the denervated part was quite abrupt — at the first glance I took it to be due to incomplete staining. But in spite of an after-staining of the vessel (supravitaly in a watch-glass) for 3—4 hours, after which time the staining became unspecific, I did not succeed in obtaining the least nerve-staining in the denervated parts.

In the *non-operated ear* normal relations were found.

90 days after the operation the last rabbit was killed. This rabbit, *in vivo* as well as upon the *histological examination*, exhibited quite the same findings as the first rabbit — nowhere in the operated ear were normal nerves to be found, in spite of very careful examination, especially of the lateral arteries.

Consequently it seemed certain that the sympathetic innervation of the blood-vessels of the rabbit's ear takes place through the peripheral nerves. For verification and in order to examine how the nerves behave when *the vessels* were sectioned, the following experiments were performed:

In 2 albino rabbits ligation and resection of about $\frac{1}{2}$ cm. of the left *arteria & vena auricularis media* at the root of the ear were performed. Ether anesthesia. The large auricular nerve was left intact. Immediately after the operation nothing special was noted except some stasis.

The day following the operation, the operated ears in both animals were

slightly cyanotic, somewhat colder than the sound ears; they were, moreover, somewhat less sensible to needle-pricks.

These phenomena disappeared after 3 and 5 days respectively. The peripheral part of the resected artery was filled with blood immediately after the operation and was clearly pulsating the day after. While the rest of the auricular vessels exhibited the usual contraction on the slightest occasion (sudden sensitive impressions, *e. g.* sudden light or noise), this was not true of the central part, about 1 cm., of the operated vessel; in both of the animals this part of the vessel kept open, was constantly $1-1\frac{1}{2}$ mm. in diameter, even when the other vessels contracted to invisibility. The rest of the artery behaved like the other vessels; these phenomena *disappeared 3 days after the operation*, after which the central part of the artery also contracted normally.

Rabbit I was killed (chloroform) 20 days after the operation and the resected artery was dissected out (from the site of the operation up to the arc) after infiltration with methylene blue. Subsequent to this the vessel was subjected to after staining in a watch-glass upon a water-bath and was under continuous observation: Everywhere upon the vessel, from the place of operation up to the arc, the vascular nerves were of normal appearance and were not to be distinguished from those of the vessel in the non-operated ear; this was the case with the nerves having free endings as well as with the reticular nerves.

Rabbit II was killed 30 days after the operation and exhibited identical relations clinically as well as histologically: The nerves of the blood-vessels in both ears were of the same appearance and number.

From these experiments I conclude that the sympathetic nerves of the blood-vessels of the rabbit's ear run from the cervical sympathetic of the same side to the vessels along the ordinary peripheral nerves. The freely ending, non-sympathetic nerves also run in these nerves.

Even though the experiments in frogs and rabbits furnished identical results, it seemed natural in the present work to examine the *vessels of the extremities*, which in any case are of most importance with reference to periarterial sympathicectomy.

Now this operation cannot be performed *lege artis* in rabbits, whose vessels are too small and thin-walled — anyhow according to my experience, even if *Wojeichowski* claims to have performed this feat; my attempts all failed. On the other hand, I thought that I could for my purpose just as well in lieu of this operation perform a simple resection of the artery; this operation must also sever possible long, perivascular tracts, and *Leriche*, too, recommends it as the "*ideal sympathicectomy*" in cases in which the circu-

lation through the vessel in question is beforehand gravely compromised. I therefore performed the following experiments:

2 brown Belgian rabbits (males). Ether anesthesia. Resection of 1—2 cm. of the right femoral artery in *trigonum Scarpae*; the vessel was ligated and the nerves and the vein left intact.

1 brown Belgian rabbit (female). Ether anesthesia. Resection of the artery as above, and in addition of a corresponding piece of the femoral vein. In all the operations, besides the adventitia, all periarterial tissue was removed, nothing being left of the sheaths of the vessels, the stumps of which were quite denuded.

No measurements of temperature or other experiments were executed on these animals as no sure conclusions as to changes in the circulation were to be drawn from extremities in which the circulation was so different from the relations in *lege artis* "sympathicectomised" arteries.

During the first days after the operation the extremities were somewhat paretic, but this symptom rapidly disappeared, and the animals thereupon behaved like sound animals.

21 days after the operation the first rabbit was killed (chloroform); in this animal only resection of the artery was performed. The nerves of the vessels were stained by methylene blue by injection through the artery and the vein peripheral to the place of operation; thereupon pieces of the excised vessels were laid on filter-paper for continued staining in incubator, other pieces were treated as usual. The results of the examination of these different pieces were identical.

The artery carried blood up to the site of operation, but seemed somewhat smaller in diameter in this place.

Upon histological examination none of the examined pieces of *femoralis*, *cruralis*, *dorsalis pedis* (besides numerous small muscle- and skin-arteries and pieces of muscle and skin) showed any change in the picture usually found — the *sympathetic nerve-nets*, especially, were everywhere beautifully stained and of quite normal appearance. Also the *nerves having free endings* were of normal appearance and number compared with those of the non-operated leg.

42 days after the operation the second rabbit was killed, in which only the artery was resected. The findings were one and all identical with those of the first rabbit — everywhere well-stained nerves, those having free endings as well as the reticular ones.

60 days after the operation the third rabbit was killed (resection of both artery and vein). This rabbit, also, had exhibited quite natural relations during the experiment — during the first days, however, stasis and slight edema of the extremity were noted.

Here, too, the relations were *histologically* quite normal — the vessels of the operated side were not to be distinguished from the normal vessels — which was as well, as I had forgotten to label the bottles and did not know which contained the vessels of the operated extremity. In no point, however, was any difference to be seen and as this was the essential point, and keeping in mind the two experiments mentioned above, I did not find it necessary to repeat the experiment.

From these experiments I conclude that neither the sensory nor the sympathetic innervation of the blood-vessels in the hind-legs of the rabbit run in long perivascular tracts, as neither resection of the artery nor of artery and vein causes the degeneration of these nerves.

The experiments recorded are, however, not quite convincing. It *might* be possible that a few of the nerve-tracts ran perivascularly, since the *number* of the nerves in the vessels compared could not be estimated with certainty. In view of this fact I performed the following experiments:

3 brown Belgian rabbits (1 male, 2 females). Ether anesthesia. Resection of the right *sciatic*, *femoral*, and some other, smaller nerves — in fact all I was able to see in a nearly full-circle incision; the stumps were ligated with fine silk; 3—4 cm. of the nerves were extirpated. All incisions healed *p. p. i.*

For the rest no experiments were executed on the animals, which all of them had paralysis of the operated leg, but no trophic disturbances whatever during the time of experimenting. One of the rabbits, however, showed symptoms of staggers, and as I did not want to give up the examination of the animal, which after spontaneous death could not, perhaps, be vitally stained, this rabbit was killed 22 days after the operation. The nerves of the vessels in the hind-legs were stained by injection through the aorta; excised pieces were treated in the usual way. *Histological findings:* Upon the larger vessels (*femoralis*, *cruralis*) I found in several places structures which resembled the previously described picture of *medullated nerves* in degeneration; the course of the nerves was, however, quite distinct in certain places, especially where the nuclei of *Schwann* were well-stained; if such a structure were followed I was frequently able to reconstruct dichotomous division, but nowhere did I succeed in demonstrating finer branches or nerve-terminations; in no place did the nerves stain well. No trace was to be seen of the *reticular nerves*, neither in the adventitia nor in the muscularis; on the other hand, nuclei were noted in several places which strikingly resembled nuclei of *Remak*; but nowhere were fibres to be seen between them — not even corresponding to the interlamellar net, which is usually most easily to be recognised after degeneration. Upon and in the walls of all the lesser vessels, arteries as well as veins and capillaries, neither nerves nor rudiments of these were seen; only in *one* place in the whole extremity was one normal nerve noted: On the most superior part of the femoral vein (*i. e.* from the middle of the thigh) one single medullated, beautifully stained

nerve was seen, which after a quite short course ended in a very beautiful *Smirnow-Dogiel* termination; the other branches in which the nerve terminated all of them ended freely in the adventitia.

35 days after the operation rabbit II was killed (chloroform). The relations were quite identical with those of the animal first killed, only no nerves at all were to be seen upon or in the walls of the vessels examined — not in the most proximal parts of the femoral artery and vein; the picture of *medullated nerves* in degeneration corresponded very nearly to that found in the first rabbit.

Rabbit III was killed 40 days after the operation. The examination showed nothing new as to the nerve-degeneration in the peripheral vessels: In this animal, also, not as much as one single normal nerve was anywhere to be seen in spite of careful after-staining in this as in the other animals. In this case I wanted to see — if possible — the transition between the denervated and the normally innervated parts of the femoral artery; I therefore immediately after the injection of stain dissected out the artery, from the middle of the thigh up to the bifurcature and stained this piece of the vessel in a watch-glass upon a water-bath. Immediately after the removal, the proximal piece of the vessel was seen normally innervated by *reticular nerves* forming a typical *plexus adventitialis*; in small pieces well-stained nerves were seen in the muscularis, too. In the distal half of the vessel, however, no nerves at all were to be seen, and I now especially studied the intermediary zone between these two parts of the artery. While no distinct zone was to be found in the adventitia, I saw the nerve-nets beautifully stained in the muscularis down to a limit which was taken to correspond to a little below the inguinal ligament. In this place the muscle-net terminated along an oblique line nearly exactly across the vessel, on the one side sending a little bayformed process with well-stained nerves further down; all of the nerve-fibres seemed to end *closed* — *i. e.* no free nerve-endings were to be seen, except in *one* place, where a faintly stained, non-medullated somewhat granulated fibre continued for about some few μ , thereupon ending abruptly; otherwise only closed meshes were to be seen.

In spite of after-staining for about one hour, after which time the staining became unspecific, this picture was the same during the whole of the observation.

From these experiments I conclude that the reticular nerves as well as the freely ending nerves of the blood-vessels in the hind-legs of the rabbit run to the periphery in the peripheral nerve-trunks and in these only.

WHAT ARE THE FUNCTIONS OF THE NERVES OF THE BLOOD-VESSELS?

I. *The nerves having free endings.*

In the anatomical part of the present work it was assumed that the freely ending nerves of the blood-vessels were of a sensory nature, as they were

frequently found connected with undoubtedly sensory structures, partly typical *Vater-Pacini* bodies, partly other structures which were taken for sensory end-corpuscles (*Smirnow-Dogiel* bodies). Now it is a very difficult thing to plan experiments which will show the function of sensory nerves. While for the motor nerves we have a certain indication of the effect of these nerves in the contraction of the innervated muscles, no such thing is to be had for the sensory nerves. Consequently this problem must as yet be considered insolvable.

Numerous surgeons declare that while it is possible to obtain complete regional anesthesia in the tissue, this is not possible for the arteries, ligation of these vessels resulting in very vivid pain; this is construed by various authors (*Brüning & Stahl*) as a proof of the existence of long perivascular, sensory tracts.

Experiments on animals have also been performed to show this; thus *Friedrich* injected concentrated solutions of lactic acid in the femoral artery of a dog; the animal reacted violently to this. The peripheral nerves of the leg were then cut and the experiment repeated — with the same result. Lastly the femoral vessels were ligated and cut, and *now* the animal did *not* react at all to the injection. According to this experiment long, sensory (pain-perceiving) tracts should exist along the vessels. Similar experiments by *Hellwig* seem to point the same way.

Such experiments I have *not* executed — also because to me they seem quite superfluous, but I have confined myself to showing:

- 1) that all larger blood-vessels are provided with nerves, which are probably sensory (*see Anatomical Part*),
- 2) that these nerve have *not* their trophic centres in the sympathetic trunk (p. 113—115) and finally
- 3) *that long, perivascular sensory tracts do not exist* (p. 115—122).

The experiments of *Friedrich* and *Hellwig* are thus to be otherwise explained, and, in addition, *Dennig* has not been able to confirm the results of these two authors.

As was evident from the *Orientation* (p. 97) the sensory nerves, besides their "essential" function (sensory, afferent), are supposed to have another function — *viz.* that of being able to act as *vasodilator nerves* by antidromic impulses. *Krogh*, however, did not succeed in demonstrating this action by stimulation of the sensory nerves of the rabbit's ear; I, too, have repeatedly tried this experiment, always with the same result: Vascular constriction, following mechanical stimulation as well as stimulation with strong galvanic or induced currents.

If, however, one waits like *Feldberg* until some weeks after the extirpation of the cervical sympathetic before conducting this experiment, the effect of the identical stimulations is invariably a *vaso-dilatation* which shows the

usual characteristics of the antidromic dilatation: A latent period, which I have seen to vary between 15 and 45 seconds, after which the dilatation fades after 3—10 minutes. That this effect is not apparent following stimulation of a freshly cut nerve with intact sympathetic, is probably due to a preponderance of the vasoconstrictor nerves running in the same trunks.

Hence, in the rabbit's ear, too, the sensory nerves are able to act as vasodilator nerves.

II. *The reticular, sympathetic nerves.*

Already the sympathetic nature of these nerves would seem to suggest that their function should be *motor*; it was mentioned in the *Orientation* that numerous investigators had obtained constrictive effect on the vessels by stimulating the corresponding part of the sympathetic. Moreover, I found by anatomical investigations that if the muscularis of the blood-vessels possesses any motor nerves at all, the reticular nerves must be the carriers of the motor impulses, as no other nerves are present in these strata; the course of these nerves in relation to the nuclei of the muscle-cells point in the same direction.

The proofs which I shall furnish for the truth of this hypothesis may be divided into *indirect* and *direct* proofs.

1. *Frog.*

A. *Indirect Proofs.*

By such I understand *functional disturbances*, which set in following the degeneration of the reticular nerves, and which may therefore be considered as *deficiency symptoms*. I shall now enter more fully into the circulatory disturbances seen in blood-vessels which by operation have been deprived of the function of the reticular nerves.

A material of 5 frogs in which the distal part of the right sympathetic had been removed (p. 113) was at hand.

Immediately after the operation the circulation was slower in the web on the operated side compared with the sound web; the circulation, however, was soon re-established and about $\frac{1}{4}$ — $\frac{1}{2}$ hour after the operation was, if anything, a little more rapid in the operated web.

24 hours after the operation the right web was distinctly reddish, with incident light as well as upon translumination. The arteries and many of the capillaries were strongly dilated, the blood stream distinctly more rapid than in the other web. The two *ranae temporariae* exhibited slight *edema* of the whole of the operated leg, including the thigh; this edema disappeared after 5 and 8 days respectively. During this time the circulation in the affected web was distinctly more rapid than in the normal web, though distinctly

less rapid than immediately after the operation. The vascular dilatation and the circulatory disturbances continued, though decreasing in degree, in 3 of the frogs (2 *temporariae*, 1 *esculenta*) until the death of the animals, 30, 50 and 60 days respectively after the operation, while in 2 frogs (both *esculentae*), after 35 and 67 days resp., I was unable to find any distinct difference in the circulation of the two webs.

The arteries immediately after the operation showed *Krogh's* local reflex of contraction after mechanical stimulation (glass-rod), the contraction frequently spreading to the whole of the visible part of the vessel. *After a certain time this reflex disappeared* and was replaced by the following: Immediately after the stimulation the usual hourglass-like contraction was visible at the point of excitation, but in lieu of spreading this constriction remained in this place without showing the slightest indication of spreading; the constriction was present for a long time — somewhat longer I thought than in a normal frog. The disturbance of reflex took place 21, 31, 12, 5, 8 days after the operation (the first-mentioned animals were not examined immediately after the operation), and the change was unaltered at the death of the animals.

While I succeeded several times in obtaining a spreading of the vascular dilatation subsequent to stimulation with *silver nitrate crystal* as used by *Krogh & Rehberg* up to 7 days after the operation, I did *not* succeed in this in any of the frogs the day they were killed.

In 10 frogs the sciatic nerve had been resected and the stumps ligated (pag. 116). These frogs also exhibited typical circulatory disturbances: The initial vascular constriction, which never failed in any of the animals treated with ganglionectomy, was not present here or only very faintly indicated — the circulation in the corresponding web only for some minutes seeming perhaps somewhat slower than in the sound web. However, 24 hours after the operation distinct vascular dilatation and more rapid circulation were noted in the operated web, even though appreciably less marked than after the ganglionectomies.

These changes persisted for 30, 32, 25, 43, 67, 39, 90 days after the operation respectively, after which time no sure difference was to be seen. 3 frogs (all *esculentae*), however, presented undoubted vascular dilatation in the affected web until they were killed, even though less pronounced than just after the operation; moreover, it was noted that one investigation might show no difference, while the next only a few days later revealed considerable difference.

As to the *spreading of contraction* after mechanical stimulation these frogs behaved just like the frogs treated with ganglionectomy: After a varying time (probably due to the varying time of examination): 16, 12, 29, 15, 22, 32, 11, 13, 24, 19 days after the operation the reflex disappeared and

after this and until the animals were killed only the local, hour-glass contraction restricted to the place of excitation was obtained; the spreading of the dilatation after chemical stimulation was not examined in these frogs.

In all of these frogs the subsequent histological examination showed the *total degeneration of the reticular nerves* — and in the frogs operated by ganglionectomy these nerves *alone* had degenerated.

It thus seems permissible to conclude *that* the demonstrated vascular dilatation and the disturbances in the reflexes must be due to the disappearance of the *reticular nerves*; *that* these nerves are the carriers of the vaso-constrictor tone for the blood-vessels in the hind-legs of the frog; and *that* these nerves are, at any rate in part, responsible for the spreading of the contraction and the dilatation subsequent to mechanical and chemical stimulation respectively. Taking these disturbances of reflexes into due consideration, it seems of less importance, that the vessels in some frogs seemed to regain their constrictor tone; as it will be discussed later under the experiments with rabbits, it may frequently look as if the blood-vessels in a sympathectomised area are not dilated compared with normal vessels, but that the abnormality of such blood-vessels can always be revealed by suitable function tests.

From these experiments I conclude that the function of the reticular nerves of the blood-vessels of the frog is motor — that these nerves are sympathetic, vaso-constrictor nerves.

In order to supply the direct proof of this assertion I shall adduce the following experiment:

B. Direct Proofs.

In 3 normal frogs the right sympathetic trunk was dissected out as indicated by Jegorow. Urethane-anesthesia. Abdominal incision. With some practice the necessary ligatures may be limited to a few — the intestines, however, must always be ligated. The sympathetic trunk is now cut through at the superior end, the connections laterally severed just as the most superior of the (on the right side comparatively few) fibres going to the aorta, the result being an about 1 cm. long nerve-stump, which is placed upon a cover glass, both webs being examined in a preparation-microscope.

The piece of nerve exposed is now stimulated by means of an induced current, just perceptible upon human skin, but no sure effect is usually seen, and the current is made stronger — until there is a plainly perceptible effect upon the human skin. Now the following facts are noted:

<i>Time:</i>	<i>0: Stimulation.</i>
(seconds)	14: A little artery just in the field of vision starts contracting. The contraction begins centrally, spreads peripherally; in the following seconds the vessel is nearly closed.

- 20: Commencing capillary contraction in several different places, other capillaries seemingly uninfluenced.
- 30: Marked capillary contraction in the whole field of vision.
- 40: Nearly all of the capillaries in the field of vision now seem contracted; the arteries are nearly closed, the blood stream arrested, except for a slow stream in the veins and in a few capillaries; in numerous places the blood corpuscles are "incarcerated" in the capillaries, which are strongly contracted in places, while the arterioles do not contain many blood corpuscles.

Upon examination of the web of the other side no distinct difference is noted from the state before the stimulation.

- 60: *The stimulation is stopped.*
- 70: As above.
- 80: do.
- 90: do.
- 100: do.
- 110: do.
- 120: The previously mentioned artery starts opening centrally.
- 130: A few capillaries start opening; general movement of the incarcerated red corpuscles.
- 160: The circulation is re-established, distinctly slower than before, through narrower vessels.
- 240: The picture nearly as before the excitation.

This experiment may be repeated 2—3 times. The other 2 frogs in which the operation succeeded, exhibited quite identical relations, the times, however, varying a little — probably because it was not possible to graduate the electrical current properly (an ordinary small induction apparatus was used). The 12—19 seconds, however, which passed between the excitation and the first perceptible effect which invariably took place in the *arteries*, was always quite constant and is also in good accord with the times found by other investigators — e. g. *Vimtrup's* 10—15 seconds.

In one of the frogs I thought I could see an indication of contraction in the vessels of *the web of the other side*, but in any case this doubtful contraction disappeared simultaneously with the cessation of the stimulation.

The experiment was now repeated in 3 of those frogs, in which the *right sciatic nerve* had previously (63, 79 and 94 days respectively) *been resected* and ligated. The sympathetic was treated as above, but in spite of stimulation with a current which at last was very strong, no indication at all of contraction was observed. This result was identical in all 3 frogs, and the

experiments were thus in good accord and went to show, *that* the sympathetic innervation of the blood-vessels in the web of the frog is motor, vaso-constrictor, *that* this impulse travels along the sciatic nerve, and *that* the anatomical substratum of the transfer of this impulse to the muscle-cells is the reticular nerves, which were found totally degenerated in all 3 animals (p. 116), these nerves being the only ones found upon the blood-vessels of the web.

As to the road by which this impulse travels (through the sciatic nerve) these experiments, however, are not convincing. Even if the connection centrally through this nerve is *trophically* necessary to prevent degeneration of these nerves, it might be supposed, that the sympathetic impulses might possibly likewise travel to the periphery *along the continuous nerve-nets of the vascular walls*. No result of the stimulation could then be expected at a time when these nets had degenerated, but in spite of this, the impulse might *normally* very well travel this way.

To clear up this question I performed the following experiment:

In 2 frogs the sympathetic was dissected out a. m. *Jegorow* and by weak and brief stimulation I secured the usual response of constriction by the vessels of the web. Thereupon the exposed sciatic nerve was cut and at

- Time:* 0: the sympathetic was stimulated with a moderately strong current.
 (seconds)
- 25: The blood stream in a little artery in the field of vision was perceptibly slower and the artery contracted a little; the contraction started centrally and spread peripherally, but the artery was not completely closed.
 - 30: The picture unchanged, the artery was not more contracted, *though the blood stream was slower than before.*
 - 40: Slow blood stream but no additional contraction of the vessels. The veins were quite unchanged in diameter, the capillaries likewise — nay, in certain places these vessels seemed to dilate a little.
 - 60: *Cessation of stimulation.*
 - 63: *A rapid blood stream immediately broke through from above, the above-mentioned artery was dilated to its previous diameter and the blood stream was rapid as before the stimulation.*

The second frog showed identical relations, and the experiment was repeated several times in both — always with the same result: not until 20—30 seconds after the stimulation a *slower blood stream*, *slight* contraction of the small arteries, *no* contraction of veins and capillaries, sometimes even slight dilatation of the capillaries.

After these experiments it might seem probable that the arteries of the web contract — even though only a little — following stimulation of the sympathetic with the sciatic cut, nor can I, after these experiments, quite exclude this possibility. Another explanation, however, seems more probable to me. During the repeated experiments I got the definite impression that the primary factor of the circulatory disturbance is *not* the arterial contraction, but that this is only seen after the circulation has slowed down — the contraction giving the impression of being rather a *result* of the slow circulation than the cause of the same.

It might also very well be supposed that the stimulation of the sympathetic acts so strongly upon the proximal vessels, which are innervated through the proximal, intact, part of the sciatic (which was cut about the middle of the thigh), that the blood stream slows down in the distal vessels, and the arteries from this cause contract a little. In harmony with this is the fact that the said contraction was always merely indicated — the strong contraction usual when the sciatic was intact was never seen; nor was as much as an indication of capillary contraction ever seen.

Hence, from these experiments, too, I conclude that the sympathetic vaso-constrictor impulses travel from the sympathetic to the blood vessels of the web *via* the sciatic nerve and from here are distributed to the reticular nerves. A weak conduction in the peri- and intravascular nerve-nets cannot be excluded, but seems improbable to me.

2. Rabbit.

Here, also, the proofs of the function of the vascular nerves may be divided into *indirect* and *direct proofs*.

A. Indirect Proofs.

I here had at my disposal 5 *albino rabbits*, in which the cervical sympathetic from the ganglion cervicale superior to the ganglion stellatum with both these ganglia had been extirpated. The rabbit's ear is especially suited for these experiments, as it is possible to follow *directly and macroscopically* changes in the diameter of the vessels and their reactions during different conditions; moreover it is possible to get a *direct measure of the amount of blood passing through the part, viz. by means of measurements of the temperature*. These measurements were always executed at a certain point of the ear and always in symmetrical places — most frequently about 3 cm. from the tip of the ear, the thermometer having its apex placed corresponding to the middle artery, whereupon the ear was rolled around it and the thermometer and ear fixed by means of a little rubber band, which was just so wide, that it was able to keep the ear *in situ* without constricting it to any extent; the rubber bands were of the same length, but anyway these measure-

ments are very rough — the error was most frequently 1—1.5⁰, this being ensured by numerous measurements in sound animals. In spite of the drawbacks, this technic was, however, quite adequate for the relations which were important in this connection.

The findings in the different animals were on the whole identical, and they are consequently best described under one head:

During the ether anesthesia the vessels in both ears dilate, equally in both. *During the operation* of ganglionectomy and during the manipulations with the sympathetic the vessels of the corresponding ear contract somewhat, but already at the close of the operation they are again dilated and clearly wider than the vessels of the opposite ear, and the ear is warmer — measurements while the animals were anesthetised, however, only revealed differences of mostly 2—3⁰.

6 hours after the operation some of the animals were examined. The blood vessels of the operated ear are now strongly dilated and pulsate much more strongly than the corresponding vessels of the other ear; the ear is red and is much warmer to the touch. The temperature is about 5—11⁰ higher than in the opposite ear. *24 and 48 hours after* the operation the same findings are revealed, but still more pronounced. The *maximum* for the vascular dilatation and the elevation of temperature lies *between 5—12 days after* the operation, in which interval differences in temperature of up to 14⁰ were recorded. In this connection, however, the absence of the contractions of *Schiff* was no doubt an important factor; these contractions had not been observed on the operated side since the operation, while the blood vessels of the normal ear might contract to invisibility upon sudden sensory impressions (light, noise, manipulations of the ear); when the animal was quit (in a box with only the head free) the temperature was, however, constant also in the sound side.

3 of the rabbits exhibited slight *edema* of the operated ear the first 1—4 days, and in 2 of these small *cutaneous and subcutaneous hemorrhages* were noted (up to the size of a shilling); these symptoms disappeared 3—6 days after the operation in all 3 rabbits. In this series of experiments hemorrhages in the later course — as described by *Lapinski* — were not observed.

All of the rabbits exhibited an undoubted vascular dilatation of all arteries of the operated ear even up to the time when the animals were killed (30, 50, 48, 38, 43 days after the operation). On comparing the size of the vessels one must not, however, be deceived by the contractions of *Schiff*, which may be very strong upon the sound side during the first minutes of the examination, while as previously mentioned, they are never to be seen in the operated ear; not until the rabbit has quieted down, can the vessels be compared. Full certainty is only arrived at by examination during anesthesia (ether) in which all central influence is excluded; several of the animals were at different times during the observation-period anesthetised, and the vessels of the two ears compared: In no case was there any doubt

but that the vessels in the operated ear were dilated compared with those of the normal ear, *except in very deep anesthesia* just prior to the death of the animals (chloroform), when the vessels seemed of equal diameter in most of the animals.

The vascular dilatation mentioned is macroscopically visible in the arteries and the veins. Of no less importance is the *behaviour of the arterioles and the capillaries*; if the rabbit's ear is placed upon the horizontal superior side of a downwardly open glass-box in which a strong source of light (*water-filter!*) is placed, even the finest capillaries may be observed in the depilated ear of albino rabbits*) through a binocular preparation-microscope. Some, especially older, rabbits have, however, too thick ears for this, but in young rabbits one may — if the light is only strong enough — dispense with all application of glycerine or oil; this is rather important as these proceedings may affect the capillaries (dilatation).

Upon comparison of the arterioles and capillaries in the two ears in *normal rabbits* no sure difference in the average diameter and the number of these vessels is to be seen.

In the *operated animals* the small blood-vessels were found in an astonishing degree to reflect the relations noted in macroscopical examination: *From the operation to the death of the animals the arterioles as well as the capillaries of the operated ear were found considerably dilated as compared with the corresponding vessels of the sound ear.* The maximum for the dilatation also here lay between 5 and 12 days after the operation, after which time the dilatation gradually decreased — varying somewhat from day to day — but always a definite difference was observed.

A feature which I have observed again and again in the sympathic-ectomised ear is the *curious, fitful, sporadical contraction of the vessels* described by Krogh in sympathicectomised frogs; while normally — and always in the non-operated ear — one observes some capillaries closing and others opening, in the operated ear one much more frequently sees *hour-glass-formed contractions*, which appear, remain for some seconds, and again disappear, while the capillaries are seldom closed over long stretches at a time. Corresponding with this the capillaries seem *more numerous* in the operated ear; similar relations to these but still more pronounced are to be seen in the *precapillary arteries*, in which such hourglass-formed contractions might remain for 10—15 minutes. These features also were unchanged at the time the animals were killed.

On the other hand, *the increased pulsation* of the vessels in the operated ear seemed to decrease during the 2—3 weeks following the operation and frequently no sure difference was seen, but especially after simultaneous

*) I am indebted to Professor, Dr. phil. A. Krogh for particularly well-suited rabbits.

rubbing or other manipulations of the ears the vessels still pulsated much more vigorously in the operated ear; this, also, was quite evident in all the animals just before they were killed.

That the seemingly regained tone of the vessels is very unstable is also revealed by the following experiment:

As is generally known, the blood pressure is considerably raised after a cold bath. If the body of a sympathicectomised rabbit about one month after the operation is submerged in cold water the following is observed: In the sound ear the arteries contract nearly to invisibility, but in the sympathicectomised ear *after 10—20 seconds is seen a strong vascular dilatation*, which only disappears after several minutes. This experiment was also performed with the same result on the rabbit which was left longest alive 50 days after the operation.

By such a test one is able to reveal the insufficiency of the regained "tone" of the blood-vessels, even if they look quite normal and to show that this "tone" is not sufficient to hold out against more pronounced changes in blood pressure, but that *blood-vessels deprived of their sympathetic innervation during these circumstances behave like slack tubes*.

The temperature. The accompanying curves (1 and 4) give an impression of the difference in the temperature of the two ears, measured in the very rough way mentioned above; the individual measurements do not present any interest, but *as a whole* the curve shows the conditions plainly enough.

In the first instance it is seen that *in the non-operated ear, too*, the temperature is somewhat raised the first days after the operation. Several investigators (*e. g. Leriche*) have thought that the corresponding finding in men after periarterial sympathicectomy is due to a *reflex-hyperemia*; this may be the case if the operation is performed under local anesthesia and if this "reflex-hyperemia" then appears just the same; after a general anesthesia another explanation seems to me at any rate just as plausible. The temperature of the human feet is, as discovered by *Ipsen*, considerably raised the first days following a general anesthesia; it might be supposed, that the rabbit's ear behaves in the same way.

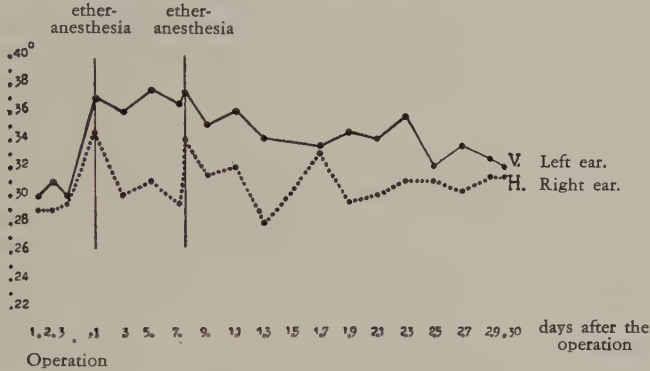
If the temperature of the rabbit's ear is examined before, during, and after general anesthesia, a rise is in all cases observed during the anesthesia; but it must be admitted that already the following day the temperature is frequently quite normal — if such a term may be used in this connection: The temperature of the rabbit's ear is very unstable; frequently, however, the temperature is somewhat raised the first days.

It is, moreover, to be seen from the curves, that, while the temperature of the sound ear varies considerably for the different measurements, in the operated ear it is quite stable, keeping at a level which is decidedly elevated as compared with the other side, even when due regard is paid to the primitive mode of examination.

It is, moreover, evident that the temperature of the operated ear does not rise considerably during a second anesthesia (*curve 1*), while the temperature of the sound ear is again somewhat raised, only to fall again during the following days. This experiment was repeated 3 times with 3

Curve I.

Temperature of rabbit's ears after left cervical ganglionectomy (p. 114).

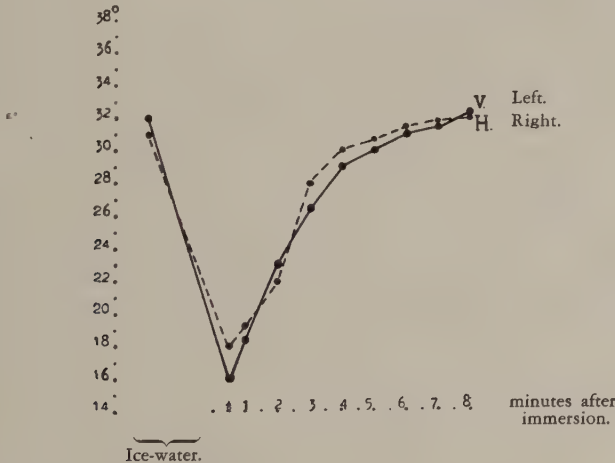


different rabbits, 6, 19, and 40 days subsequent to the operation — always with the same result.

The curves, moreover, show that the temperature of the sound ear sometimes, in the time following the operation, reaches figures equalling those

Curve II.

Temperature of normal rabbit's ears 5 minutes after immersion in ice-water.

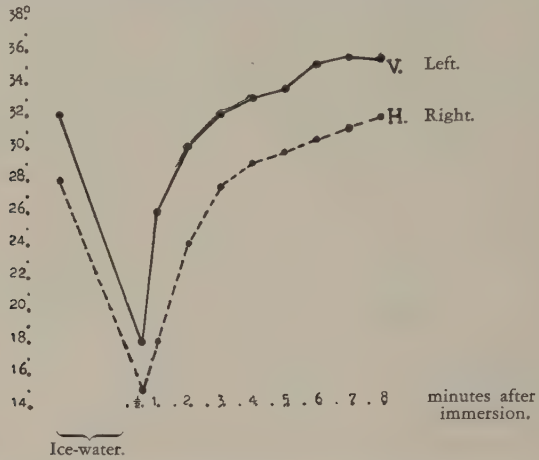


of the operated ear; this was of course also to be expected, as the examination must sometimes coincide with a physiological dilatation of the auricular vessels; that this has not more frequently been the case is probably due to the contractions of the vessels during the manipulations of measurement.

I have, moreover, tried the reactions of the auricular vessels to *cold*, analogously with *Ipsen's* test in man. These results are also to be considered with some reservation as the mode of measurement is very rough. The ears were held in running water (10—15°) for 5—6 minutes, or immersed

Curve III.

Temperature of denervated rabbit's ears after immersion in ice-water, 81 days after resection of the afferent nerves on the left side.

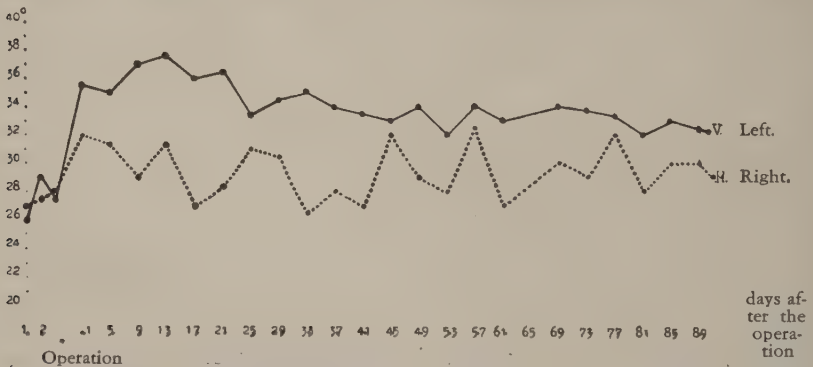


in ice-water for a similar time, and the temperature of the ears for the following about 10 minutes recorded, until the ears were as warm — frequently warmer — than before the experiment.

On all the occasions when the experiment was tried with *normal* rabbits

Curve IV.

Temperature of rabbit's ears after resection of the afferent nerves on the left side.



(*curve 2*) the two ears showed a certain similarity in the rapidity with which the temperature rose.

On the 5 occasions when the experiment was tried (in 4 rabbits) with

the *operated animals* the results were identical (*curve 3*): The operated ear became not so cold as the sound ear, and it reacted much more rapidly and strongly during the subsequent rise of temperature.

Besides the material already referred to I shall mention the 4 (3) albino rabbits in which *the peripheral nerves for the left ear had been resected and ligated*.

These rabbits behaved entirely like the ganglionectomised animals, and I can consequently refer the reader to the description of these. In these rabbits, also, the vascular dilatation and the elevation of temperature did not *quite* disappear, even if both these symptoms *decreased in degree* until the death of the animals 30, 60, and 90 days after the operation.

The rabbit which lived longest (*curve 4*) during the whole of the observation showed, if decreasing, yet definite elevation of temperature in the operated ear, and the difference in reaction to cold was also very pronounced 81 days after the operation (*curve 3*). The arterioles and the capillaries of these animals, too, behaved like those of the ganglionectomised rabbits.

These experiments seem to furnish a good supplement to the degeneration experiments mentioned at p. 117 and do not leave any doubt but that the sympathetic innervation of the blood-vessels — *and the whole of this innervation* — runs to the rabbit's ear in the peripheral nerves.

It must, however, be stressed that the temperature-measurements performed are very rough examinations, which do not present any interest by themselves; added to the other symptoms, however, I think a certain importance attaches to them and for that reason only are they mentioned in this work.

B. Direct Proofs.

The poles of a small induction-apparatus are connected with two large, semicircular surgical needles passed through a little rubber-stopper at a distance of about $\frac{1}{2}$ cm. from each other. The needles are now applied one on each side of the middle artery of a rabbit's ear at about its base, and the current is made (plainly to be felt upon human skin). Immediately an hourglass-formed contraction of the artery is seen at the place of excitation and *a few seconds later* this contraction spreads as well centrally as peripherally, the vessel being contracted almost to invisibility. If the current is broken off, the vessel dilates *in one moment* to its full previous diameter, *e. g.:*

- Time:* 0: The current is made, the artery about 2 mm. broad.
 (seconds) Immediately an hourglass-formed contraction is seen at the point of excitation.
 5: The contraction has spread several mm. in both directions.
 10: About half of the artery is strongly contracted, is about $\frac{1}{2}$ mm. broad; at the place of excitation the contraction is at its height, the artery is quite closed and invisible.

- 20: The whole of the artery up to the arch is strongly contracted.
- 30: Unchanged. *The current is switched off.*
- 35: The whole of the artery is again quite open, about 2 mm. broad.

This experiment may be repeated *ad infinitum*.

If now this experiment is performed upon a rabbit's ear whose sympathetic, reticular nerves have degenerated, quite another reaction is seen: The *only* visible effect is the local, now more *annular*, contraction, which remains sharply defined for as long as the excitation lasts, disappearing the very moment the stimulation is discontinued. At no time of the experiment does the rest of the artery contract in spite of the blood stream being quite arrested by the annular contraction (in one case the temperature measured over the superior part of the artery, as described at p. 129, fell as much as 1° after some minutes' stimulation).

I never succeeded in getting any effect whatever in the small arteries or the capillaries neither in normal nor in denervated ears; the blood stream slows down, but in no case was any unquestionable contraction noted.

These experiments seem to supplement *Krogh's* experiment on the spreading of vascular contraction in arteries of the frog's web (*pag.* 125), and one must assume that also the reticular nerves of the blood-vessels of the rabbit's ear have a *motor, vasoconstrictor function* and are responsible for the spreading of the contraction after stimulation; these nerves *possess tone* and even if denervated blood-vessels may in a certain measure regain this tone inasmuch as the paralytic phenomena decrease in degree, such a re-established 'tone' is easily exposed and its insufficiency demonstrated.

SPECIAL PROBLEMS

"Vasomotor Nerves".

In the present work the term "*vasoconstrictor nerves*" has been applied to the reticular, sympathetic nerves; this would seem permissible since these nerves are then named after their most evident function.

However, it deserves to be stressed that these nerves *have equally a vasodilator function*. This is apparent *e. g.* in psychically determined vasodilations and may be ascribed to an *inhibition of tone in the centres of the sympathetic*; a vasodilatation of this kind may also be assumed to follow the stimulation of the central stump of a cut sensory nerve (the *Lovén-reflex*).

One should thus be able to distinguish between *two* forms of nervously conditioned vasodilatation, *viz.*:

1. The *sympathetically* conditioned vaso-dilatation (*inhibition of tone*) and
2. the *antidromically* conditioned vaso-dilatation (by *antidromic conduction in sensory nerves*).

As a matter of fact, these two forms of vaso-dilatation can be clearly distinguished from each other.

The first form of vaso-dilatation is known *e. g.* from the rabbit's ear as following upon the rhythmical contractions of *Schiff*: Immediately after the contraction a vaso-dilatation may occur, but this dilatation may *in an instant* be succeeded by a maximal contraction caused by a new sensory impulse (pain, light, noise). Here the antidromic impulses in sensory nerves cannot explain the vaso-dilatation, this mechanism partly having a rather long latent period, and partly disappearing very gradually (after several minutes) — its disappearance being supposed to depend upon the elimination of vasodilator substances by means of the blood-stream.

This mechanism cannot be active in the vaso-dilatation mentioned here, which is also known from humans, in whom strong psychical impressions may effect very rapid changes of calibre in the arteries as well as the capillaries of the skin.

While thus a nervously conditioned *vascular constriction* is only known to be effected in *one way viz.* by *strengthening the vaso-constrictor tone of the reticular, sympathetic nerves*, vaso-dilatation may be assumed to be ef-

fects in two ways: Partly through *inhibition of tone in the sympathetic nerves*, partly by *antidromic conduction in sensory nerves* (liberation of H-substance?).

Consequently the sympathetic nerves of the vessels are not only to be considered as *vasoconstrictor nerves* but as *vasodilator nerves as well*, and the most suitable name for them seems to me to be the old name: *The vasomotor nerves*. That the sensory nerves of the vessels — as sensory nerves elsewhere — may perhaps, under certain conditions, act as vasodilator nerves is another matter but, however large the rôle ascribed to this antidromic conduction in the responses of the organism to injuries, these sensory nerves do not in my opinion on that account deserve name of vasomotor nerves *sensu strictiori*.

The term vasomotor nerves may then with a certain justice be reserved for the *sympathetic, reticular nerves*, which alone have any intimate relation to the muscle-cells of the blood-vessels, and which by their action alone may produce vaso-constriction as well as vaso-dilatation.

But now the question presents itself: May the sympathetic, vasomotor nerves be assumed to be able to act as vasodilators, when a suitable stimulation acts upon the nerves *peripherally to the sympathetic trunk*?

This should not *a priori* seem excluded, even though very little evidence as yet exists for the support of this hypothesis. The only fact which may be adduced is Krogh's spreading of vaso-dilatation subsequent to weak, mechanical stimulation of the blood-vessels of the frog's web and tongue, which was thought to be due to an *axon-reflex in sensory nerves*. Now the anatomical investigations, also in the present work, show that even if sensory nerves are frequently to be found in the vicinity of the small blood-vessels, no such nerves are present upon the vascular wall itself.

If antidromic conduction in sensory nerves was active in this experiment, a certain latent period was to be expected, but Krogh found that only a few seconds passed between stimulation and dilatation. Moreover, the experiments described at p. 125 go to show that this reflex is, at any rate in part, of a sympathetic nature.

For the explanation of this experiment two possibilities present themselves:

1. An axon-reflex in sensory nerves runs through peripheral anastomoses into the sympathetic nerves and inhibits their tone, the result being a vaso-dilatation.
2. Weak mechanical stimulation tends to inhibit the tone of the sympathetic nerves.

It is in good accord with this last contingency that strong mechanical stimulation is invariably followed by a vaso-constriction, but this might also

be explained by the first possibility. Which, if any, of these possibilities is the correct one seems difficult to determine now; the whole view taken in these remarks is rather hypothetical, and I shall therefore not enter more fully into these speculations in this place.

Tonus.

Lastly I shall briefly discuss how it may be brought about that denervated blood-vessels may to a certain extent regain their tone.

In the introduction to the present work a pronouncement by *Leriche* was cited, in which he supposes the existence of *peripheral ganglion cells*, which might maintain the function of the sympathetic nerves and take over the control of the tone of the blood-vessels subsequent to operations which sever the connection with the sympathetic. As shown in p. 113—115 *these ganglion-cells and "peripheral vasomotor centres of III order" do not exist*. Moreover, it was shown in p. 129 that blood-vessels which are quite robbed of their nerves *do not entirely regain their tone*, as they were always found dilated as compared with the normal vessels of the other side. On the other hand, denervated vessels might *to a certain extent react to cold and warmth*, and there is no doubt but that the initial vasodilatation decreases much in the course of time — that the paralytic symptoms decrease in degree, as already *Langley* observed.

Now as this cannot be due to any action of nerves, one must suppose, as *Langley* did, that the partial regaining of tone must be due to properties in the muscle-cell itself (*"the inherent contractile power of the plain muscular tissue itself"*).

The continuous vaso-constrictor tone, which is normally maintained by means of the sympathetic nerves, must effect certain continuous metabolic processes in the muscle-cell; when this tone is suddenly discontinued either by section of the nerves or by ganglionectomy, it would not seem too improbable to suppose that the muscle at first as it were "runs amok". Only when the cell has adapted itself to regulate the (catabolic and anabolic?) processes in the muscular protoplasm necessary to a certain medium-contraction without nervous control, can the balance be re-established to a certain extent, and a certain degree of contraction be maintained, when not too large demands are made upon this "tone".

Whether this power of regaining a certain degree of tone may be ascribed to *Boeke's* "*periterminal network*" or to any definite morphological factor at all, must be left to future investigations.

SUMMARY OF PHYSIOLOGICAL PART

- 1) The reticular nerves of the blood-vessels described in the anatomical part of the present work are of a *sympathetic* nature and have their trophic centres in the corresponding sympathetic trunk; their function is mainly that of *vasoconstriction*, and they possess *vasoconstrictor tone*; the reticular nerves found on the capillaries are of the same nature and have the same function.
- 2) The reticular, sympathetic nerves may, by their function alone, effect *vasoconstriction as well as vasodilatation* in the innervated blood-vessels; consequently these nerves alone seem to deserve the name of *vasomotor nerves sensu strictiori*.
- 3) *Peripheral ganglion-cells*, which might be supposed to be able to maintain the vasoconstrictor tone, or possibly take over the control of this tone after removal of the centres in the sympathetic trunk, do not exist in the blood-vessels of the extremities.
- 4) Blood-vessels whose sympathetic nerves have degenerated, do not entirely regain their tone, but keep dilated up to 90 days after the sympathetic ganglia have been extirpated or the connection of the vessels with the latter has been severed; such vessels may always be "exposed" by a function test. The temperature of thus sympathicectomised areas is continually (90 days) elevated as compared with the sound side.
- 5) The freely ending nerves of the blood-vessels described in the anatomical part of the present work are *not* of a sympathetic nature. They may, under certain conditions, function as vasodilator nerves by antidromic conduction, but are not on that account considered to deserve the name of vasomotor nerves *sensu strictiori*. It is probable that these nerves are identical with *sensory nerves*.
- 6) The reticular as well as the freely ending nerves of the blood-vessels of the extremities run from the centre to their fields of innervation *via* the peripheral nervetrunks, and *long, perivascular tracts (motor or sensory) do not exist*.
- 7) These conclusions only apply to the animals and the parts of the body on which the experiments have been performed. The histological investigation does not, however, furnish any evidence against the supposition that the innervation of the blood-vessels in corresponding parts of nearly related organisms is identical.

III.

MODE OF ACTION
OF PERIARTERIAL SYMPATHICECTOMY

— iam provideo animo, velut qui proximis
litori vadis inducti mare pedibus ingrediuntur,
quicquid progredior, in vastiorem me altitu-
dinem ac velut profundum inveni, et crescere
pæne opus, quod prima quæque perficiendo
minui videbatur.

T. Livius, lib. xxxi.

THE operation known as "periarterial sympathectomy", originally introduced by *Jaboulay* in 1899, has only gained ground in surgical circles throughout the world since the recent works of *Leriche*.

As *Jaboulay* performed the operation it really was "periarterial" — *i. e.* only the periarterial tissue was removed. As the operation is now performed the whole of the adventitious coat of the artery is removed in addition, right down to the muscularis, and the importance of this is strongly stressed by *Leriche*. The tissue is removed by dissection at varying lengths, most frequently for about 10 cm., usually upon one of the large arteries of the extremities (*brachialis, femoralis*).

Handley has proposed to destroy the nerves of the adventitia by injecting 70 p. c. alcohol into the adventitia, *Lauwers* bathes the artery in a solution of ammonia. *Brüning*, in addition to the adventitia, removes the whole of the vascular sheath and moreover — operating on the *femoralis* — resects the saphenous nerve.

Originally the *purpose* of this operation was to sever the vaso-constrictor nerve-tracts for the extremities, these being supposed to run in the outer parts of the arterial wall.

In normal arteries the *primary effect* of this proceeding is a strong vascular contraction at the site of operation — the artery may contract to half of its original diameter; this contraction seems, to the naked eye at any rate, to be quite local — if pieces of undamaged artery are left between the sympathectomised parts, the vessel presents the appearance of a rope of pearls.

After the lapse of a varying time (always, however, within the first 24 hours) the *secondary effect* appears: a hyperemia of the whole of the extremity concerned. It has in many cases been demonstrated that this hyperemia is an *active hyperemia* and is accompanied by elevation of temperature and enlargement of the pulse-wave as measured by the oscillogram of *Pachon*, and it seems beyond all doubt that the secondary effect of this operation — at any rate for a time — is an increased blood-flow through the extremity. This increased blood-flow is utilised in various maladies, in which the blood-supply of the extremity is unsatisfactory or in cases where other reasons make such an added blood-supply desirable.

The *clinical aspect* of the matter I shall leave alone in the present work; for this I may refer the reader to one of the numerous large works which

have been published on this very subject *e. g.* *Ipsen's* critical appreciation of the modern surgery of the sympathetic (1927).

It shall, however, be mentioned that the opinions as to the effectiveness of the operation have been rather divided; thus *Baron* (1923) says: "*Die Heilerfolge der periarteriellen Sympathectomie sind auf Autosuggestion des Arztes und des Kranken, auf Bettruhe und auf Proteinkörperwirkung zurückzuführen*". On the other hand, numerous surgeons swear by the operation, and it cannot be denied, that most remarkable results have been achieved. That periarterial sympathectomy has been regarded with extraordinary interest — perhaps least in this country — is apparent from the overwhelming wealth of communications, not all perhaps equally critical, which have of recent years appeared on the subject.

It would be impossible to give an account of all these communications here; in the present work only the principles of the matter will be discussed and for the clinical evidence I must refer the reader to the more lengthy communications by *Leriche*, *Läwen*, *Wiedhopf*, *Brüning*, *Brüning & Stahl*, *Hahn* and *Ipsen*. In these works an excellent material with demonstrations of the effect of the operation is to be found, illustrated by clinical observations as well as by temperature-measurements (*Ipsen*), by oscillometry and by several other methods of investigation.

On the basis of these communications it may be taken for granted that the effects described as following the operation, effects which may best be summed up under the term *increased blood-flow*, as they are all consequences thereof, really occur in most of the cases. Some cases, however, do not present these symptoms, these cases most frequently being found in elderly people, whose blood-vessels in several ways seem to react differently to those of younger people, and in cases in which the operation is performed upon arteriosclerotic vessels.

The divergence of opinion does not really appear until it is to be explained *how* these effects are brought about, and it is to be determined *how long they last*. Most of the investigators now seem united in the opinion that the effects are *not* lasting; in most of the recent works the hyperemia is stated to decrease after 3—8 weeks, and I for one cannot help thinking that when a few workers record elevation of temperature several years after the operation, it is due to a defective technic of measurement.

As to the mode of action itself the original explanation of *Jaboulay* and *Leriche* was that the long, perivascular, vaso-constrictor nerve-tracts, which were supposed to run in the adventitia of the vessel, were severed by the operation.

As previously mentioned this theory must now be considered obsolete, even if *Leriche* seems to support it in some of his previous works. *Hohlbaum*, too, is nearly of the same opinion, even if he thinks that the vessels distal

to the site of operation are not quite robbed of sympathetic influence, the vaso-constrictor nerves being able to act through anastomoses.

Brüning (1924) maintains a somewhat different stand-point, as he supposes, that in addition to the periarterial innervation the blood-vessels are provided by vaso-constrictor nerves segmentally from the peripheral nerve-trunks: "*Es gelangen also zu den Gefäßen der Extremitäten sympathische Bahnen einmal durch Vermittlung spinaler Nerven, aber auch unmittelbar*". He now thinks that the vaso-constriction, which he observes following upon a shot-lesion of the sciatic, is due to a reflex, the nerve scar being the starting-point of the afferent part of the reflex arc, the other part being the long, perivascular, vaso-constrictor tracts. These are severed by periarterial sympathicectomy and the heightened constrictor-tone is thereby discontinued. According to this theory the mode of action of periarterial sympathicectomy would be a *weakening* of the vaso-constrictor impulses, a part of the vaso-constrictor nerves, including the connection centrally along the artery, being removed by the operation.

This explanation is also embraced by *Seifert* and *Kulenkampf*; *Kappis* shares the same views but he thinks that in addition a *mechanical* factor may be active, the arteriolysis itself contributing to the hyperemia.

To this theory of *Brüning's* I shall in the first place remark that it is compatible with the facts elicited by histological investigations: A periarterial connection centrally *may* be surmised along the continuous nerve-nets which are found upon and in the vessels (*rete interlamellare, rete musculare*). It is not proved, however, that vaso-constrictor impulses are able to reach the blood-vessels along this road; quite contrarily *Schilf* (1924) saw no plethysmographic effect upon the distal parts of the blood-vessels of an extremity after excitation of the exposed periarterial tissue around the femoral artery; on the contrary in some cases he saw a *vaso-dilatation*, which, however, disappeared after section of the *crural nerve*. Moreover; it does not tend to make a periarterial conduction probable that the primary effect of periarterial sympathicectomy, the constriction of the artery operated upon, never spreads distally or centrally, though it may be objected to this that the excitation may not have been adequate or perhaps not strong enough. Lastly the experiments described in *p. 128* seem to point in the opposite direction.

Against *Schilf's* and my own observations *Leriche & Policard's* previously mentioned observation of capillary constriction in the nail-fold during the execution of a periarterial sympathicectomy seems a somewhat slight weapon, and in his later works (1925) *Brüning* too seems to have left this explanation. He now concedes that the sympathetic innervation of the blood-vessels takes place segmentally along the peripheral nerve-trunks; on the other hand, he supposes that the vaso-constrictor tone of these nerves is maintained by *continuous, afferent impulses*, which are conducted centrally from the vascular wall *along long, perivascular, sensory nerve-tracts*. By periarterial

sympathicectomy these tracts are sectioned, fewer impulses reach the centre, the vaso-constrictor tone of the area is diminished, and the result is a hyperemia.

This theory is accepted by *Kreibich* and *Schamoff*, and it is supported by the previously mentioned experiments of *Friedrich* (p. 123), which tended to show the probability of long, afferent tracts along the blood-vessels. Similar experiments have been executed by *Hellwig*, who after having performed periarterial sympathicectomy upon the femoral artery (in animals), injected a 5 p. c. solution of chloride of barium into the artery peripheral to the site of operation; after this he *once* saw a slight reaction of pain and *once* no reaction, injection upon the sound side always resulting in a strong reaction. *Ritter* came to the same conclusion, observing reaction of pain when he ligated a larger artery in animals; if he then ligated the vessel peripheral to the first ligature, the animal did not react at all. *Abrashanow* (1927) repeated *Friedrich's* experiment with the same result.

The long, perivascular, afferent tracts should, according to these experiments, seem certain enough; neither *Dennig* nor *Odermatt*, however, were able to find evidence of the existence of such tracts by similar experiments. As has already been mentioned above, all these experiments seem superfluous and unconvincing to me; the proof of the existence of long, perivascular tracts can only with full certainty be given through *combined anatomical and physiological investigations*, in which the persistence of these tracts is demonstrated after the section of all nerve-trunks to the extremity. The results of such investigations (*Lapinski* 1905, the present work p. 115—122) have been identical: *Long, perivascular, afferent tracts do not exist*, and consequently this theory, too, breaks down.

One must then hope for theories compatible with the existing anatomical and physiological fact that the afferent as well as the efferent nerves of the blood-vessels of the extremities run in the peripheral nerve-trunks, and in these only.

In accordance herewith *Läwen* supposes that the effect of periarterial sympathicectomy is due to a *reflex*; he thinks that the *reparative processes in the afferent nerves* of the vascular wall, which he supposes are damaged by the operation, give rise to an *excitation* of these nerves, and this excitation is now conducted centrally through the same nerves, resulting in a *centrally conditioned vaso-dilatation*, the other part of the reflex arc being the "vaso-dilator nerves" — which nerves are meant by this term is not mentioned. In other words, *Läwen* takes a sort of *Lovén-reflex* to be the cause of the hyperemia following periarterial sympathicectomy.

With this theory it would seem quite compatible that the hyperemia after this operation is *most frequently temporary*, and that its duration is recorded by many surgeons to be the 2—4 weeks which such reparative processes will probably take. A more enduring effect in some cases might be due to a *formation of neuromes* in the damaged nerve-stumps, all the

more so since such neuromes are really known to have given rise to vaso-motor disturbances, and it may thus be probable that they may give rise to a reflex.

On the other hand, mutually agreeing communications from a number of surgeons, especially from Germany, in which country the amputation-neuromes are so deplorably in evidence since the war, seem to show that the effect of such a reflex originating in a neurome in the large majority of cases is a *vaso-constriction*, which is promptly removed by the removal of the neurome or by "icing" the neurome (*Läwen, Wiedhopf, Lehmann*).

Läwen does not mention which reparative processes he takes to be the factors causing the reflex after periarterial sympathectomy, but his theory cannot *a priori* be rejected.

Another explanation, which also makes use of the afferent nerves, is the one put forward by *Lehmann* in 1924. *Lehmann* thinks that the tone of the vasoconstrictor nerves is maintained by continuous, afferent impulses, which, however, leaving the vessels segmentally reach the centre from the periphery along the ordinary sensory nerve-trunks. Periarterial sympathectomy now acts by destroying part of these nerves, the impulses of these nerves are discontinued, and the total number of impulses reaching the centre is consequently diminished; hence the vaso-constrictor tone, too, is diminished, and the result is a hyperemia ("*Wird ein Teil der sensiblen Bahnen ausgeschaltet oder gelähmt, so werden auch die vaso-konstriktorischen peripherwärts geleiteten Erregungen vermindert und der Erregungszustand dieser Zentren herabgesetzt. Dieser Vorgang äussert sich in dem Entstehen der Hyperämie*").

Hahn, too, embraces this theory and it must also be conceded that it possesses some rather prepossessing features. It is in good accord with the anatomical facts, it is compatible with the conceptions of tone current in physiological circles, and the disappearance of the sympathectomy-effect may without constraint be explained by the regeneration of the affected afferent nerves after a certain time.

Now *Lehmann* himself has communicated a case in which the sciatic nerve, about 10 years previous to the observation, had been sectioned at about the middle of the thigh, and later on trophical disturbances had set in, viz. paralysis of the foot with atrophy of the muscles, anæsthesia and ulcers under the foot. Previous to the observation *periarterial sympathectomy* had been performed upon the femoral artery, and following this operation the ulcers of the foot healed, only, however, to reappear 3 months after the operation. Now *Lehmann* operated the patient and found an apple-sized neurome upon the central end of the sciatic; the neurome was "iced" *a. m. Läwen* and the next day the leg was considerably warmer than the other leg — the patient spontaneously remarked that the subjective sensation of warmth was quite similar to that following the sympathectomy. Objec-

tively, too, hyperemia and elevation of temperature of the extremity was found, *also in the anesthetic areas*; this hyperemia persisted for 2—3 days, thereupon decreasing gradually, but the operated leg was still warmer than the other leg when the patient was in a warm room, while in a cold room it was cold and painful. *Lehmann* adds another similar observation (neurome of the *tibial* nerve), in which the hyperemia following the "icing" persisted for 8 days.

Now, *how is this hyperemia to be explained?* According to common opinion the whole number of vasomotor nerves in the blood-vessels of the extremity should long since have degenerated, the sciatic having been sectioned 10 years previously and being found discontinued at the operation. How then can the blood-vessels react with hyperemia?

Before this question is answered, I shall briefly mention two theories which may be of importance in this connection.

Wiedhopf (1924) performed periarterial sympathectomy on the femoral artery of a dog; the leg was examined plethysmographically. Neither during nor after the operation was any trace of effect noted with this technic. When, however, he "iced" the sciatic nerve the effect was a marked increase of volume of the corresponding leg.

In humans, too, *Wiedhopf* demonstrated that the vaso-constrictor nerves must run in the peripheral nerves, since by injection of novocaine in the ulnar and the median nerve he saw a considerable increase of volume of the hand by plethysmography.

As an explanation of the hyperemia following a periarterial sympathectomy *Wiedhopf* now supposes that the initial contraction of the artery operated upon gives rise to an anemia of the vascular wall in this place; when the constriction disappears, this place is unable to withstand the blood-pressure and is consequently dilated, this being the cause of the hyperemia.

This theory does not seem plausible and has I think been abandoned by most workers.

On the other hand, *Ipsen* (1927) has put forward a theory, which he himself only calls a weakly supported working-hypothesis. *Ipsen* in the first instance stresses that some *vasa vasorum* are certain to be destroyed by the operation — sometimes so many that *gangrene* of the arterial wall sets in — but in all cases a certain number. The media is consequently frequently influenced in a way which may be pronounced a *lesion*. Now it is a well-known fact from physiology, that a damaged place in a muscle becomes negatively electrical in relation to the neighbouring musculature: "*Without insisting that exactly this takes place when the nutrition of the musculature is influenced by the removal of the vasa vasorum, I should be inclined to think that similar relations obtain in sympathectomy. From the place of the lesion, one might think, an effect was propagated through the nerve-net, resulting in a diminishing of tone in the artery, at any rate compared with the sound artery, and that this is the explanation of the dilatation*". *Ipsen*

supposes, that "*sympathicectomy does not sever nerve-tracts in the adventitia, but it compromises the nutrition of the media, thereby giving rise to a change in the tone of the nerve-net*".

As to *Lehmann's* cases, *Ipsen* thinks that they can only be explained by supposing that the nerve-net of the vascular walls may persist after section of the sciatic, but as will be evident from the investigations of *Lapinski* and from the experiments published in the present work, this conception is untenable.

If it might be supposed, however, that the impulse assumed by *Ipsen* was able to spread in the muscle of blood-vessels *without the aid of the nerve-net* — when this had degenerated, this theory might explain the observations of *Lehmann*, but such a mode of thought meets with certain difficulties: Very little is at present known as to the conduction from muscle-cell to muscle-cell in denervated musculature. The experience described in *p. 135—136* seems to speak against such a conduction: Even when using very strong excitation I never succeeded in seeing the least spreading of the annular constriction of the denervated middle artery of the rabbit's ear.

The cases of *Lehmann*, too, may conceivably be explained otherwise: For, when the sciatic was sectioned, the peripheral parts of the blood-vessels of the extremity in question were certainly without any nerves whatever, but the proximal parts of the vessels still received their innervation through the *femoral nerve*, which was intact and the most proximal parts of the vessels moreover from the sympathetic directly. If therefore the (hypothetical) continuous, afferent impulses, which are conducted centrally from the neurome present, are responsible for the abnormally strong constrictor-tone, this tone, at any rate in *the vessels of the proximal parts of the extremity*, may be supposed to diminish reflexly. The distal parts are denervated — *i. e.* they behave like slack tubes towards a greater elevation of blood-pressure, their diameter being strongly dependent upon the pressure in the afferent arteries, and when this pressure is raised by the aforementioned reflex-effect upon the proximal vessels, the result will be a hyperemia — *also of the anaesthetical areas*.

That this is more than a theory may be demonstrated by the following experiment: If a rabbit, whose cervical sympathetic (including the stellate ganglion) has been removed some time previously, is placed in cold water, the vessels of the sound ear will contract; in the operated ear, however, the denervated vessels will dilate (*p. 133*).

For the explanation of the mode of action of periarterial sympathicectomy in blood-vessels whose innervation is intact, the following three theories then seem compatible with the anatomical and physiological facts:

1. *Läwen's* theory: By the operation *sensory nerves* are damaged upon and around the vessel; the reparative processes in the nerve-ends become the starting-place of *afferent impulses* which centrally inhibit

the vaso-constrictor tone. The efferent part of the reflex-arc may be supposed to be:

- a) *the sympathetic, vaso-constrictor nerves,*
- b) *the "vaso-dilator nerves" (Läwen).*

The hyperemia is discontinued, when the reparative processes end.

2. *Lehmann's theory:* By the operation a certain number of the afferent, sensory impulses from the vessels and their vicinity are discontinued; as the vaso-constrictor tone is supposed to be maintained by these impulses and is held to be proportional with their number and their intensity, this tone decreases, the result being a hyperemia. The efferent part of the reflex-arc is also here the sympathetic vaso-constrictor nerves. *The hyperemia is discontinued, when the sensory nerves are regenerated or when the centre has accommodated itself to the diminished number of impulses.*
3. *Ipsen's theory:* By the operation the nutrition of the media is compromised, as part of the *vasa vasorum* is destroyed. The place of operation becomes negatively electrical as to the surrounding part of the artery, and becomes the starting-point of an excitation which results in a diminishing of the tone of the peripheral nerve-net, the result being a hyperemia. *The hyperemia disappears when the lesion of the artery is healed — i. e. when the place of operation is no longer electrically different from its surroundings.*

All these 3 theories are quite compatible with the anatomical and physiological facts, and certain reasons speak for each of them.

While the two first-mentioned theories both of them rest upon the supposition of a *reflex*, this is not the case with the theory of *Ipsen*.

Now certain relations seem to indicate that a reflex really is active in periarterial sympathicectomy, inter alia the observation, made by several surgeons, that after this operation hyperemia sometimes sets in not only in the operated extremity, but even in that of the opposite side — nay, in some cases in all four extremities (*Leriche*).

If this is really correct, it points directly to a reflex-action, as such a process may easily be imagined to irradiate centrally, while, as mentioned above, a spreading in the peri- and intravascular nerve-nets seems less probable and the theory of *Ipsen* — if the afore mentioned observations are correct — will consequently seem less probable.

There remain *Läwen's* and *Lehmann's* theories. The mechanism in the two theories is essentially the same, the only difference being that the one supposes the decreasing of tone to be due to an *excitation*, the other supposing that the cause is more probably a diminution of the number of afferent

impulses — *i. e.* a sort of paresis. Moreover *Läwen* assumes that the efferent impulses go through the “vaso-dilator nerves” — if by these he is thinking of the sensory nerves, both parts of the reflex-arc will be sensory. This seems a rather improbable thought, even if it is not quite impossible. Even if thus *Läwen*'s theory is not entirely to be excluded, *Lehmann*'s explanation seems most compatible with common physiological mode of thought.

At the present moment I think it most probable that the explanation of the mode of action of periarterial sympathicectomy is to be sought in this theory.

FINAL SUMMARY

The object of the present work is, by anatomical and physiological investigations, to contribute to the knowledge of the peripheral innervation of the blood-vessels of the extremities, with especial reference to periarterial sympathectomy.

I. *Anatomical Part.*

In an historical introduction the previous investigations on vascular innervation are described.

In the section entitled Technic the vital staining of nerves by means of methylene blue (*Ehrlich*) is discussed, and a modification of this method based upon supravital staining at reduced pressure and subsequent staining under oxygen-pressure is communicated.

From the anatomical investigations it appears:

1. That the peripheral innervation of the blood-vessels examined with the technic employed exhibits no fundamental histologically recognisable difference in the animals examined (frog, guinea-pig, rabbit, man);
2. that the blood-vessels of the animals examined are in the whole of their course provided with nerves;
3. that these nerves may be divided, morphologically, into two groups:
 - a) Nerves having free endings, which are most frequently medullated to their terminations, which are to be found on larger vessels only and only in the outer layers of the vascular wall (*adventitia*), while they are never found in the deeper layers; these nerves have been seen in connection with unquestionably sensory structures. Similar nerves are frequently found in intimate relation to smaller vessels, even the capillaries, but in that case never on the vascular wall itself;
 - b) nerves, which are always non-medullated, whose arrangement in the walls of the blood-vessels is characterised by the formation of peripheral nerve-nets and whose finest ramifications seem to end in a closed net of neuro-fibrils, which is probably placed *extracellularly* between the individual muscle-cells, touching these opposite their nuclei;
4. that nowhere in the described nerve-nets was it possible to find any indication of a separation in segments or zones which might be neurogenically separated, but that the peripheral nerve-nets of the vascular wall

may be supposed to form one continuous nerve-net throughout the whole of the vascular system;

5. that the histological substratum for an innervation of the *Rouget* cells of the capillaries is present, nerves having been observed touching these cells opposite their nuclei;
6. that peripheral typically sympathetic ganglion cells have been found on certain small vessels (precapillary arteries) belonging to the visceral system, while no such cells have ever been found on vessels from the extremities, neither small nor large.

II. *Physiological Part.*

In an orientating introduction the various views of the physiology of the vascular innervation are briefly stated, and the three previously executed combined anatomical-physiological investigations (*Lapinski, Eugling, Woollard*) are described. Of these *Eugling's* results do not seem convincing.

From the investigations undertaken it appeared that

- 1) the reticular nerves of the blood-vessels described in the anatomical part of the present work are of a sympathetic nature and have their trophic centres in the corresponding sympathetic trunk; their function is mainly vaso-constriction, and they possess vaso-constrictor tone; the reticular nerves found on the capillaries are of the same nature and have the same function;
- 2) the reticular, sympathetic nerves may, by their function alone, effect vaso-constriction as well as vaso-dilatation in the innervated blood-vessels; consequently these nerves alone seem to deserve the name of vasomotor nerves *sensu strictiori*;
- 3) peripheral ganglion cells, which might be supposed to be able to maintain the vaso-constrictor tone, or possibly take over the control of this tone after removal of the centres in the sympathetic trunk, do not exist in the blood-vessels of the extremities;
- 4) blood-vessels whose sympathetic nerves have degenerated do not entirely regain their tone, but remain dilated up to 90 days after the sympathetic trunk has been extirpated or the connection with it severed; such vessels may always be "exposed" by a function test. The temperature of thus sympathectomised areas is continually (90 days) elevated as compared with the sound side;
- 5) the freely ending nerves of the blood-vessels described in the anatomical part of the present work are not of a sympathetic nature. They may function as vaso-dilator nerves by antidromic conduction, but are not on that account considered to deserve the name of vaso-motor nerves *sensu strictiori*. They are probably identical with ordinary sensory nerves;

- 6) the reticular as well as the freely ending nerves of the blood-vessels of the extremities run from the centre to their fields of innervation *via* the peripheral nerve-trunks, and long perivascular tracts do not exist;
- 7) these conclusions only apply to the animals and the parts of the body on which the experiments have been performed. It would seem, however, to be a reasonable working hypothesis that the innervation of blood-vessels in corresponding areas in the other organisms examined in the present work is identical, since the histological conditions furnish no evidence for assuming a difference.

III. Finally an account is given of the theories put forward as to the mode of action of periarterial sympathicectomy. No final result can be arrived at on the basis of the facts available, but it would seem that the theory first put forward by *Lehmann* is most probable. This theory states that in periarterial sympathicectomy a certain number of the afferent sensory impulses from the vessels and their surroundings will be discontinued. As the vasoconstrictor tone is supposed to be maintained by these impulses proportionally with their amount and intensity, this tone will be diminished subsequent to the operation, and the result will be hyperemia. This hyperemia may be supposed to be discontinued upon regeneration of the sensory nerves, or when the centre has adapted itself to the diminished number of impulses.

RESUME

Formaalet med dette arbejde er gennem anatomisk-physiologiske undersøgelser at yde et bidrag til kendskabet til den perifere kar-innervation paa extremiteterne, særlig til belysning af den periarterielle sympathectomi.

I. *Anatomisk Del.*

I en historisk indledning gøres rede for de tidligere undersøgelser over kar-innervationen.

I afsnittet „Teknik“ diskuteres den vitale nervefarvning med methylenblaat (*Ehrlich*), og der meddeles en modification af denne farvemetode baseret paa supravital farvning ved hjælp af undertryk og ilt-tryk.

Af de anatomiske undersøgelser fremgaar det:

- 1) At den perifere kar-innervation undersøgt med den anvendte teknik ikke frembyder principielle, histologisk erkendelige forskelle hos de undersøgte dyr (frø, marsvin, kanin, menneske).
- 2) At der paa karrene i deres hele forløb findes nerver.
- 3) At disse nerver morfologisk kan deles i to grupper:
 - a) Frit endende nerver, som oftest er marvholdige, som kun findes paa større kar og da i de ydre lag af karvæggen (*adventitia*), mens de ikke er fundet i dybere lag. Disse nerver er set i forbindelse med utvivlsomme sensitive dannelser. Lignende nerver findes ofte i intim relation til mindre kar, ogsaa capillærer, men da aldrig paa selve karvæggen;
 - b) nerver, som altid er marvløse, hvis anordning i karvæggen er karakteriseret af perifere netdannelser og hvis fineste forgreninger synes at ende i et lukket net af neuro-fibriller, som sandsynligvis forløber extracellulært mellem de enkelte muskelceller, som de berører paa højde med kærnen.
- 4) At man i de skildrede nervernet intetsteds fandt tegn til en adskillelse i segmenter eller zoner, som muligt kunde være neurogent adskilte, men at de perifere nervernet kan tænkes at danne eet ubrudt netværk gennem hele kartræet.
- 5) At det histologiske substrat for en innervation af de *Rouget'ske* celler er tilstede, idet cellerne berøres af nerver i højde med kærnen.

- 6) At der paa smaa kar (præcapillære arterier) tilhørende det viscereale system er fundet perifere, typisk sympathiske ganglieceller, men at saadanne aldrig er fundne paa kar fra extremiteterne, hverken smaa eller store.

II. *Physiologisk Del.*

I en orienterende indledning refereres kort de forskellige opfattelser af kar-innervationens physiologi, idet der nærmere gøres rede for de tre tidligere udførte kombineret anatomisk-physiologiske undersøgelser (*Lapinski, Engling, Woollard*); af disse synes *Engling's* resultater ikke overbevisende.

Af de foretagne undersøgelser fremgaar det:

- 1) De paa karrene fundne netdannende nerver er af sympathisk natur og har deres trofiske centrum i den samsidige truncus sympathicus. Deres funktion er vasoconstriction, og de har vaso-constrictorisk tonus. De paa capillærerne fundne netdannende nerver er af samme natur og har den samme funktion.
- 2) De sympathiske netdannende nerver kan ved deres funktion alene fremkalde saavel vaso-constriction som vaso-dilatation i de innerverede kar, hvorfor alene disse nerver menes at kunne betegnes som vaso-motoriske nerver sensu strictiori.
- 3) Perifere ganglieceller, som kunde tænkes at overtage den vaso-constrictoriske tonus efter bortfald af centrene i truncus sympathicus eksisterer ikke for extremitetskarrenes vedkommende.
- 4) Kar, hvis sympathiske nerver er degenereret genvinder ikke deres tonus helt, men forbliver dilaterede indtil 90 dage efter at truncus sympathicus er fjernet eller forbindelsen dermed afbrudt; saadanne kar kan altid „afsløres“ ved en belastningsprøve. Temperaturen paa saaledes sympathectomerede partier ligge vedvarende (90 dage) højere end paa den normale side.
- 5) De paa karrene frit endende nerver er ikke af sympathisk natur. De er i stand til at virke som vaso-dilatatoriske nerver ved antidrom ledning, men menes ikke derfor at kunne betegnes som vaso-motoriske nerver sensu strictiori. Det er sandsynligt, at de er identiske med almindelige sensitive nerver.
- 6) Saavel de netdannende som de frit endende nerver til extremitetskarrene forløber fra centrum til deres innervationsomraade gennem de perifere nervestammer og lange perivasale baner eksisterer ikke.
- 7) Disse slutninger gælder kun for de dyr og de legemsdele paa hvilke eksperimenterne er udførte. Det synes dog en rimelig arbejdshypothese, at innervationsforholdene i kar i tilsvarende gebeter hos andre af de i dette arbejde undersøgte organismer er de samme, idet de histologiske forhold ikke giver grund til at antage en forskel.

III. Endelig gøres der rede for de fremsatte teorier om den periarterielle sympathectomi's virkemaade. Det er ikke muligt at komme til et endeligt resultat paa basis af de foreliggende kendsgerninger, men det synes som om den først af *Lehmann* fremsatte teori har størst sandsynlighed for sig. Denne teori gaar ud paa følgende: Ved den periarterielle sympathectomi bortfalder et vist antal af de afferente sensitive impulser fra karrene og deres omgivelser; da den vaso-constrictoriske tonus antages opretholdt ved disse impulser og proportional med deres mængde og intensitet, formindskes denne tonus efter operationen og følgen bliver en hyperæmi. Denne hyperæmi kan formodes at bortfalde, naar de sensitive nerver er regenererede eller centrum har indstillet sig paa det formindskede antal impulser.

RÉSUMÉ

Le présent ouvrage a pour but de contribuer, par des recherches anatomiques et physiologiques, à étendre notre connaissance de l'innervation périphérique des vaisseaux, pour mettre notamment en lumière la sympathectomie périartérielle.

I. Partie anatomique.

Les recherches antérieures traitant de l'innervation des vaisseaux sont exposées dans une introduction historique.

La partie "technique" discute de la coloration vitale des nerfs au moyen du bleu de méthylène (*Ehrlich*) et il y est exposé une modification de cette méthode de coloration, basée sur la coloration hypervitale, à l'aide d'un procédé avec dépression d'air et pression d'oxygène.

Il ressort des recherches anatomiques :

1. que l'innervation périphérique des vaisseaux, dans la technique employée, ne présente pas chez les animaux examinés (grenouille, cobaye, lapin, homme) de différences fondamentales, histologiquement saisissables.
2. que les vaisseaux sont pourvus des nerfs dans toute leur étendue.
3. que ces nerfs peuvent être divisés morphologiquement en deux groupes :
 - a) Des nerfs librement terminés et qui, le plus souvent, contiennent de la moelle. Ils ne se trouvent que dans les vaisseaux d'une certaine importance et dans les couches extérieures de la paroi du vaisseau. (*adventitia*). Par contre, ils n'existent pas dans les couches plus profondes. Il a été constaté que les nerfs sont joints à des formations qui sont indubitablement sensitives. On trouve souvent des nerfs analogues qui accompagnent des vaisseaux des moindre importance, parfois même des capillaires, mais dans ce cas, ils ne sont jamais fixés sur la paroi même du vaisseau.
 - b) Des nerfs qui sont toujours sans moelle et dont la disposition dans la paroi du vaisseau est caractérisée par la formation de réseaux périphériques et dont les plus petites ramifications semblent aboutir à un réseau fermé de neuro-fibrilles qui passent vraisemblablement entre les différentes cellules musculaires qu'elles touchent au niveau du noyau.

4. que les réseaux de nerfs décrits ne comportaient aucun indice permettant de conclure à une division en zones ou segments pouvant être séparés neurogéniquement, mais, on est porté à croire que les réseaux de nerfs périphériques forment une suite continue de réseaux passant par le système vasculaire tout entier.
5. que le substratum histologique nécessaire à une innervation des cellules de *Rouget* se trouve établi puisque les cellules sont touchées par des nerfs au niveau du noyau.
6. qu'on a trouvé sur de petits vaisseaux, (artères pré-capillaires) appartenant au système viscéral, des cellules ganglionnaires périphériques typiquement sympathiques, mais que de telles cellules ne sont jamais trouvées sur des vaisseaux, grands ou petits, provenant des extrémités.

II. Partie physiologique.

Les différentes conceptions de la physiologie de l'innervation des vaisseaux ainsi que les trois recherches combinées (anatomiques et physiologiques) déjà entreprises (*Lapinski, Eugling, Woollard*), sont brièvement exposées dans l'introduction; les résultats auxquels est arrivé *Eugling* ne semblent pas convaincants.

Il ressort des recherches entreprises :

1. que les nerfs qui forment des réseaux et qui ont été trouvés sur les parois des vaisseaux sont de nature sympathique et qu'ils ont leur centre trophique dans le tronc sympathique du côté correspondant. Ce sont des vaso-constricteurs, et ils ont une tonicité vaso-constrictrice. Les nerfs formant réseau, trouvés sur les capillaires, sont de même nature et ont les mêmes fonctions.
2. que les nerfs sympathiques formant réseau peuvent, par leur fonctionnement, provoquer aussi bien vaso-constriction que vaso-dilatation dans le vaisseau innervé; c'est pourquoi ces nerfs seulement peuvent être qualifiés de vaso-moteurs dans le sens étroit du mot.
3. qu'il n'existe pas dans les vaisseaux des extrémités de cellules ganglionnaires périphériques qui pourraient se charger de la tonicité vaso-constrictrice après la suppression des centres du tronc sympathique.
4. que les vaisseaux dont les nerfs sympathiques ont dégénéré ne recouvrent pas entièrement leur tonicité mais restent dilatés jusqu'à 90 jours après que le tronc sympathique ait été enlevé ou que la liaison avec lui ait été interrompue; la présence de tels vaisseaux peut toujours être révélée par un essai de tension. La température des parties sympathectomisées de la sorte reste (90 jours) plus élevée que pour le côté normal.
5. que les nerfs qui se terminent librement sur des vaisseaux ne sont pas de nature sympathique. Ils sont capables d'agir comme vaso-dilatateurs par contre-courant mais on n'estime pas qu'ils puissent pour cela être

- qualifiés de nerfs vaso-moteurs dans le sens étroit du mot. Il est probable qu'ils sont indentiques aux nerfs sensitifs ordinaires.
6. que les nerfs formant réseaux aussi bien que ceux qui se terminent librement, sont logés dans les faisceaux de nerfs périphériques sur leur trajet du centre à leur champ d'innervation et qu'il n'existe pas de longs trajets périvasculaires.
 7. que ces conclusions ne sont valables que pour les animaux et les parties du corps sur lesquelles les expériences ont porté. Il paraît pourtant admissible d'adopter l'hypothèse suivant laquelle les conditions d'innervation des vaisseaux dans les domaines correspondants des autres organismes examinés dans cet ouvrage, seraient identiques, étant donné que les conditions histologiques ne font supposer aucune différence.

III. Nous donnons enfin un exposé des théories émises concernant le mode d'action de la sympathectomie périartérielle. Les faits présents ne permettent pas d'aboutir à un résultat définitif, mais il semble que la théorie présentée pour la première fois par *Lehmann* soit la mieux fondée. Voici en quoi cette théorie consiste: Par la sympathectomie périartérielle, on supprime un certain nombre d'impulsions sensitives afférentes provenant des vaisseaux et de leurs alentours; comme il est admis que la tonicité vaso-constrictrice est maintenue au moyen de ces impulsions et qu'elle est proportionnée à leur quantité et à leur intensité, cette tonicité est diminuée après l'opération dont la conséquence est une hyperhémie. Il est à supposer que cette hyperhémie cesse lorsque les nerfs sensitifs sont régénérés, ou lorsque le centre s'est accommodé au nombre d'impulsions diminué.

RÉSUMÉ

Die Absicht dieser Arbeit ist durch anatomisch-physiologische Untersuchungen einen Beitrag zur Kenntniss der periferen Gefässinnervation der Extremitäten zu leisten, besonders zur Beleuchtung der periarteriellen Sympathectomie.

I. Anatomischer Teil.

In einer historischen Einleitung wird über die früheren Untersuchungen über Gefässinnervation Rechenschaft abgelegt.

Im Abschnitt "Technik" wird über die vitale Nervenfärbung, mit Methylblau (*Ehrlich*) diskutiert, und eine Modifikation dieser Färbmethode auf supravitale Färbung mit Hilfe von Unterdruck und Sauerstoffdruck wird mitgeteilt.

Aus den anatomischen Untersuchungen geht hervor:

1. Dass die periphere Gefässinnervation mit der angewendeten Technik untersucht, keine principiellen, histologisch erkennbaren Unterschiede bei den untersuchten Tieren (Frösche, Meerschweinchen, Kaninchen, Menschen), ergibt.
2. Dass sich auf den Gefässen in ihrem ganzen Verlaufe Nerven finden.
3. Dass sich diese Nerven morphologisch in 2 Gruppen teilen lassen:
 - a) Frei endende Nerven, die öfters markhältig sind, die sich nur auf grösseren Gefässen finden und da in den äusseren Schichten der Gefässwand (*adventitia*), während sie sich in den tieferen Schichten nicht finden. Diese Nerven hat man in Verbindung mit unzweifelhaft sensitiven Bildungen gesehen. Aehnliche Nerven findet man oft in Relation zu kleineren Gefässen, auch Capillären, doch aber nie eben auf der Gefässwand;
 - b) Nerven die immer marklos sind, deren Anordnung in der Gefässwand von periferen Netzbildungen charakterisiert ist und deren feinste Verzweigungen in einem geschlossenen Netz von Neuro-Fibrillen zu enden scheinen, die wahrscheinlich extracellulär zwischen den einzelnen Muskelzellen verlaufen, welche sie auf der Höhe der Kerne berühren.

4. Dass man in dem geschilderten Nervenetz nirgends Zeichen von einer Trennung in Segmente oder Zonen fand, welche möglicherweise neurogen getrennt sein könnten, aber man kann sich denken, dass das periphere Nervenetz ein ununterbrochenes Netz durch den ganzen Gefässstamm bildet.
5. Dass das histologische Substrat für eine innervation der *Rouget'schen* Zellen vorhanden ist, da die Zellen von Nerven in der Höhe des Kernes berührt werden.
6. Dass auf kleinen Gefässen (präcapillären Arterien) dem visceralen System angehörig, periphere, typisch sympathische Ganglienzellen gefunden wurden, aber dass solche nie auf Gefässen von Extremitäten, weder klein noch gross gefunden werden.

II. Physiologischer Teil.

In einer orientierenden Einleitung werden kurz die verschiedenen Auffassungen der Physiologie der Gefässinnervation referiert, indem über die drei früher ausgeführten, kombiniert anatomisch-physiologischen Untersuchungen (*Lapinski, Engling, Woollard*) Rechenschaft gelegt wird; von diesen scheinen *Engling's* Resultate nicht überzeugend zu sein.

Aus den vorgenommenen Untersuchungen geht hervor:

1. Die auf den Gefässen gefundenen netzbildenden Nerven sind von sympathischer Natur und haben ihr trophisches Centrum in dem gleichseitigen Truncus sympathicus. Ihre Funktion ist Vasoconstriction, und sie haben vasoconstriktorischen Tonus. Die auf den Capillären gefundenen netzbildenden Nerven sind von gleicher Natur und haben die gleiche Funktion.
2. Die sympathischen netzbildenden Nerven können durch ihre Funktion allein sowohl Vaso-Constriction als Vaso-Dilatation in den innervierten Gefässen hervorrufen, weswegen man meint allein diese Nerven als vaso-motorische Nerven sensu strictiori, bezeichnen zu können.
3. Periphere Ganglienzellen von denen man sich denken könnte, dass sie den vaso-constriktorischen Tonus nach Wegfall der Centren im Truncus sympathicus übernehmen, existieren was die Extremitäten anbelangt nicht.
4. Gefässe deren sympathische Nerven degeneriert sind, wiedergewinnen ihren Tonus nicht ganz, aber verbleiben dilatiert bis zu 90 Tagen, nachdem der Truncus sympathicus entfernt ist, oder die Verbindung mit ihm abgebrochen ist; solche Gefässe können immer durch eine Belastungsprobe "entschleiert" werden. Die Temperatur auf solchen sympathectomierten Partien liegt andauernd (90 Tage) höher als auf der normalen Seite.
5. Die auf den Gefässen frei endenden Nerven sind nicht von sympathischer Natur. Sie sind im Stand als vaso-dilatatorische Nerven bei Anti-

- dromleitung zu wirken, aber man meint nicht sie deshalb als vasomotorische Nerven sensu strictiori bezeichnen zu können. Es ist wahrscheinlich, dass sie mit gewöhnlichen Sensitivnerven identisch sind.
6. Sowohl die netzbildenden als die frei endenden Nerven zu den Extremitätsgefässen verlaufen vom Centrum zu ihren Innervationsgebieten durch die periferen Nervenstämme, und lange perivasale Bahnen existieren nicht.
 7. Diese Schlüsse gelten nur für die Tiere und die Körperteile auf welchen die Experimente ausgeführt sind. Es ist doch eine wahrscheinliche Arbeitshypothese, dass die Innervationsverhältnisse in Gefässen entsprechender Gebiete bei anderen von in dieser Arbeit untersuchten Organismen die gleichen sind, da der histologische Verhalt keinen Grund gibt einen Unterschied anzunehmen.

III. Endlich wird für die aufgestellten Theorien über die Arbeitsart der periarteriellen Sympathectomie Rechenschaft gelegt. Es ist nicht möglich auf Basis der vorliegenden Tatsachen zu einem endgültigem Resultat zu kommen, aber es scheint dass die zuerst von *Lehmann* aufgestellte Theorie die grösste Wahrscheinlichkeit bietet. Diese geht auf folgendes hinaus: Bei der periarteriellen Sympathectomie fällt eine gewisse Anzahl der afferenten sensitiven Impulse von den Gefässen und ihrer Umgebung weg; da man annimmt, dass der vaso-constrictorische Tonus bei diesen Impulsen aufrechterhalten wird und proportional mit ihrer Menge und Intensität ist, wird dieser Tonus nach der Operation vermindert, und die Folge davon ist eine Hyperämie. Diese Hyperämie wird vermutlich wegfallen, wenn die sensitiven Nerven regeneriert sind, oder sich das Centrum auf eine verminderte Anzahl Impulse eingestellt hat.

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II & III. NERVES OF THE BLOOD-VESSELS: PHYSIOLOGY & MODE OF ACTION OF PERIARTERIAL SYMPATHICECTOMY

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PLATES

Figure 1.

Nerves having free endings from the adventitia of the aorta of the frog.

The nerves are seen terminating in the bud-like endings described in p. 58. The branches marked = ended in the same way, but in different planes.

Drawn from the fresh preparation, stained supravitaly in a 0.01 p. c. solution of methylene blue.

Figure 2.

Rete interlamellare of palatine artery of the frog.

Downwards in the preparation the nuclei of the muscle-cells are stained; in the middle of the picture is seen the interlamellar nerve-net, provided with nuclei of *Remak* at the points of division; the fibres are distinctly fibrillous, form rhomboidal meshes, which are placed parallel to the axis of the vessel; to the right a larger nerve-trunk; the vessel is surrounded by chromatophores.

The preparation stained by intracardial injection and subsequent staining upon slide (see p. 48). Fixed in the usual way.

One year after the preparation the stain was good, though not as fine as previously.

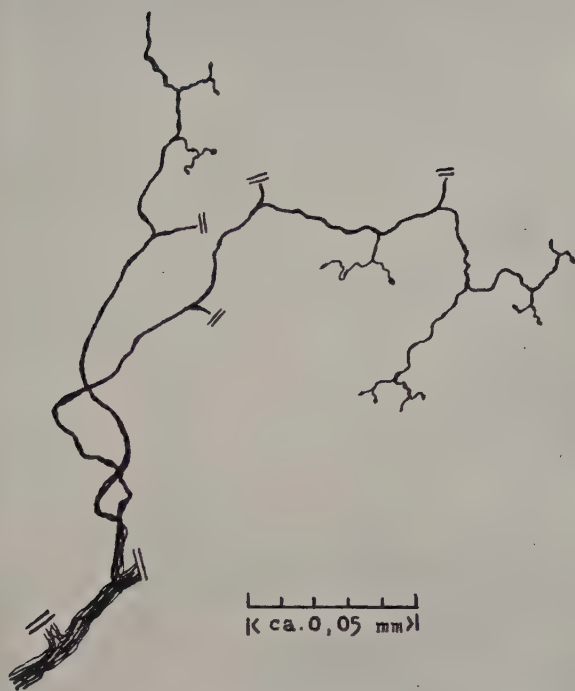


Figure 3.

Reticular nerves upon a small artery of the abdominal wall of the frog.

Upwards in the picture the nuclei of the muscle-cells are stained; downwards the *plexus adventitialis* is focussed, which in vessels of this size consists of 5—15 μ thick bundles of non-medullated nerves, each bundle containing only a few fibres, running along the vessel, connected with each other by bundles of about the same thickness; from this plexus considerably thinner nerves (of which there is a faint suggestion downwards in the picture) pass inwards to form the *rete musculare*.

The preparation stained by intracardial injection and after-stained as described in p. 48. Fixed in the usual way.

One year after preparation the stain was unchanged.

III/39.

Figure 4.

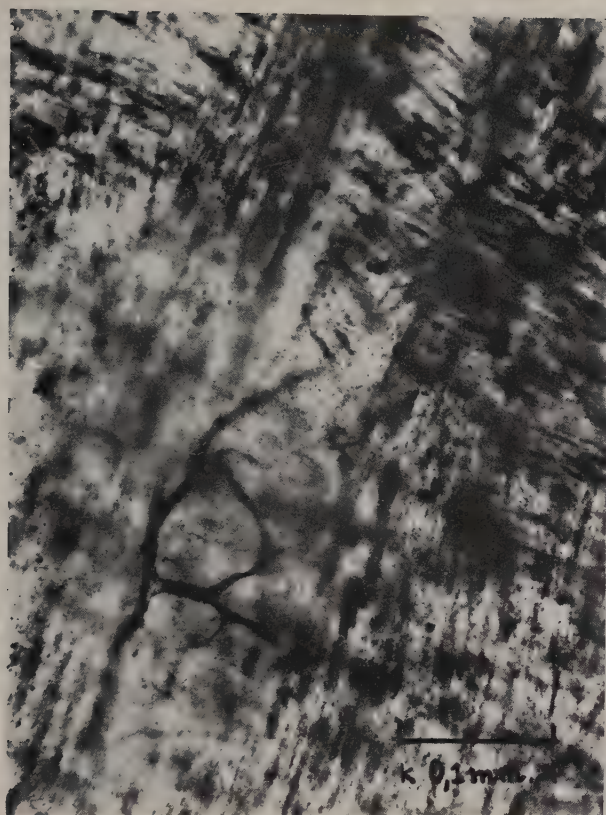
Reticular nerves upon precapillary artery of the frog's tongue.

Two muscle-cells are seen upon the vessel, the peripheral one lies somewhat obliquely across the vessel (probably it is such a staining of muscle-cells upon a small artery seen at slight magnification which *Glaser* figures as "*nerve-spiral around a capillary*"). To the right along the artery two non-medullated nerves, which in the middle of the picture approach each other and in this place one of them divides into two; at the points of division nuclei of *Remak* — to the left a compact Y-shaped one. Across the upper part of the picture a larger nerve-bundle (which more to the right in the preparation was connected with the nerves of this artery).

The preparation stained by injection of 1 p. c. solution of methylene blue in the lymph-sack; after-staining as described in p. 48. Fixed in the usual way.

One year after preparation the stain was unchanged.

III/80.



*Figure 5.**Capillary nerves from the frog's tongue.*

At top to the right a precapillary artery runs downwards and inwards, then divides into two capillaries; in the artery and in the inferior capillary red corpuscles; across the vessels branches from the sensory plexus of the mucous membrane; in the middle of the picture branches go off from these nerves to join the nerves of the capillaries, these being almost invisible in the photograph.

The preparation stained supravitaly on slide. Fixed in the usual way.

One year after preparation the stain was passable.

III/38.

*Figure 6.**Capillary nerves from the dorsum pedis of the frog.*

Capillary net from the skin; downwards some red corpuscles, otherwise the vessels are empty. Along the capillaries non-medullated nerves of distinctly fibrillous appearance, provided with nuclei of *Remak*; staining of the nuclei of the *Rouget*-cells, whose protoplasm was only faintly stained in the preparation. No free terminations.

The preparation stained by subcutaneous injection of a 0,01 p. c. solution of methylene blue; after-staining on slide. Fixed in the usual way.

3 months after preparation the faint stain of the protoplasm of the *Rouget*-cells disappeared; 5 months later the nerve-staining had nearly disappeared, while one year after preparation the nuclei of the *Rouget*-cells still kept the stain.

III/33.

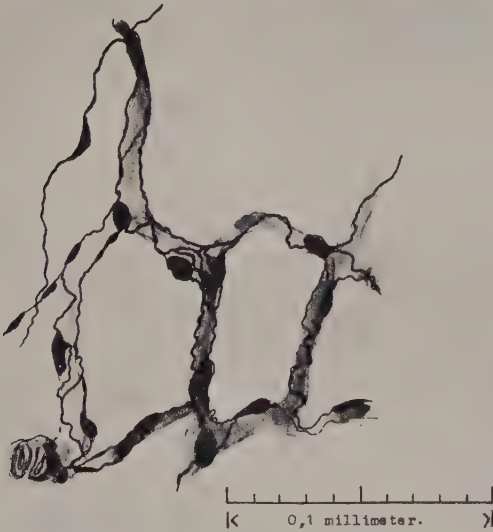


Figure 7.

Reticular nerves upon artery of the mesentery of the guinea-pig.

The artery runs longitudinally in the field of vision, is barely $\frac{1}{4}$ mm. broad; upwards an accompanying larger nerve crosses the artery; in the middle of the picture the meshes of the *rete interlamellare* are seen running longitudinally; the meshes of the *rete musculare* running transversely are faintly suggested deeper down; in the middle of the right margin of the picture a nerve is seen passing inwards upon the artery; in the preparation itself this nerve was seen dividing into the interlamellar net at about the middle of the field of vision.

The preparation stained and fixed as described in p. 46.

One year after preparation the stain was unchanged.

IV/5.

Figure 8.

Drawings (by means of Abbe's apparatus) from fixed preparations.

- a) *Capillary nerves* from the *amnion* of the guinea-pig; a single nucleus of *Remak*, otherwise only the small ovoid enlargements are seen, in several places of the annular appearance ("Endösen"?) described in p. 61.
- b & c) *Capillary nerves* from the same place.
- d) *Encapsuled "sensory" end-corpuscle* (see p. 74) from the rabbit's crural artery. The corpuscle is 0,07 mm. long.
- e) *Encapsuled "sensory" end-corpuscle* from the aorta of the rabbit, about 0,15 mm. long.

The preparations stained and fixed as described in p. 46.

One year after preparation the stain was nearly quite faded.

IV/14 & 22 & II/27 & 43.

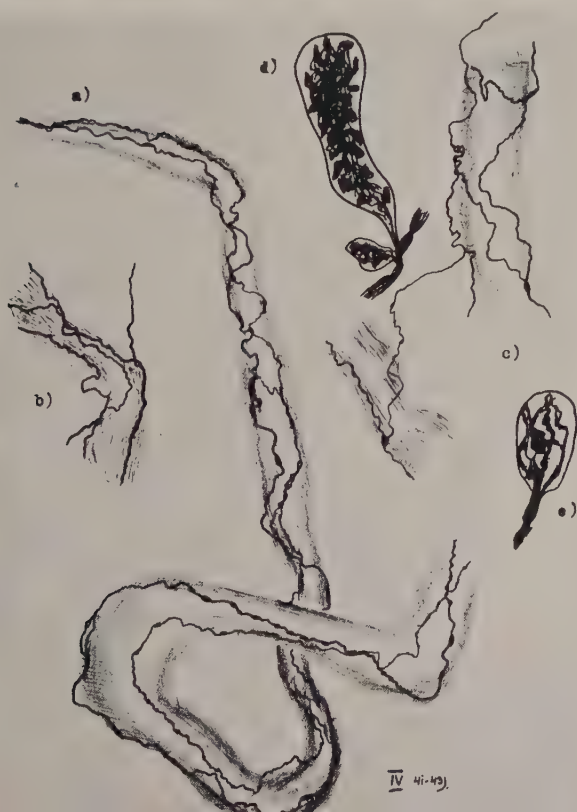


Figure 9.

Art. auricularis media from rabbit's ear.

The vessel fills the whole of the field of vision. Across it runs the sympathetic *plexus adventitialis*, characterised by the large anastomoses, into which the whole thickness of the nerve-bundle enters; the bundles are about $15\ \mu$ (the preparation was lost before exact measurement could be made).

Upwards to the left a rabbit's hair.

The preparation stained and fixed as described in p. 46.

The preparation was lost shortly after it was made.

II/73.

Figure 10.

Rete interlamellare from the crural artery of the rabbit.

The vessel fills the whole of the field of vision. The muscle-cells are partly stained and show through as a back-ground to the picture; the large nerve-trunk upwards to the left belongs to the *plexus adventitialis*; by strongly compressing the preparation I succeeded in bringing it into the same plane as the interlamellar nerve-net, after which it was possible to photograph this nerve giving off branches to this nerve-net.

Stained and fixed as described in p. 46.

9 months after preparation the stain was unchanged.

II/147.

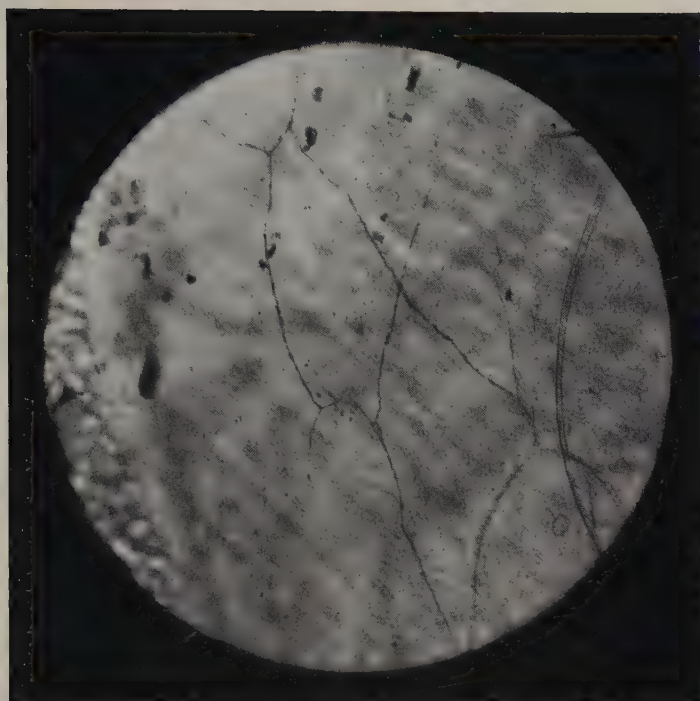


Figure 11.

Freely terminating (sensory) nerves of the auricular artery of the rabbit's ear.

The nerves originate in a larger trunk downwards to the left in the preparation (hidden by the fat cells) and reach the vessel at a right angle; arrived upon the artery the trunk divides into two branches which both run across the axis of the vessel and during further division disappear round the curve of the artery; the coarser branches are given off at an acute (*left branch*), the finer at an obtuse angle (*right branch*); both of the branches ended in *Smirnow-Dogiel* end-platelets, which are below the plane of the photograph. The *breadth* of the vessel is about 2,1 mm.

The preparation stained and fixed as described in p. 46.

One year after preparation the stain of the nerves was unchanged; the end-platelets, however, were much faded.

II/79.

Figure 12.

Freely terminating (sensory) nerves of the peroneal artery of the rabbit.

Downwards a nerve-trunk is seen winding round the artery; in the middle of the picture it divides dichotomously into numerous branches, all of which end freely in the adventitia; coming from the right another, larger, nerve-trunk reaches the vessel (to end, higher up in the preparation, in the same way). Staining of the nuclei of the muscle-cells upon the little branch which goes off to the right, not of the cells of the artery itself.

The *breadth* of the vessel is about 0,9 mm.

The preparation stained and fixed as described in p. 46.

One year after preparation the stain was quite lost.

II/87.

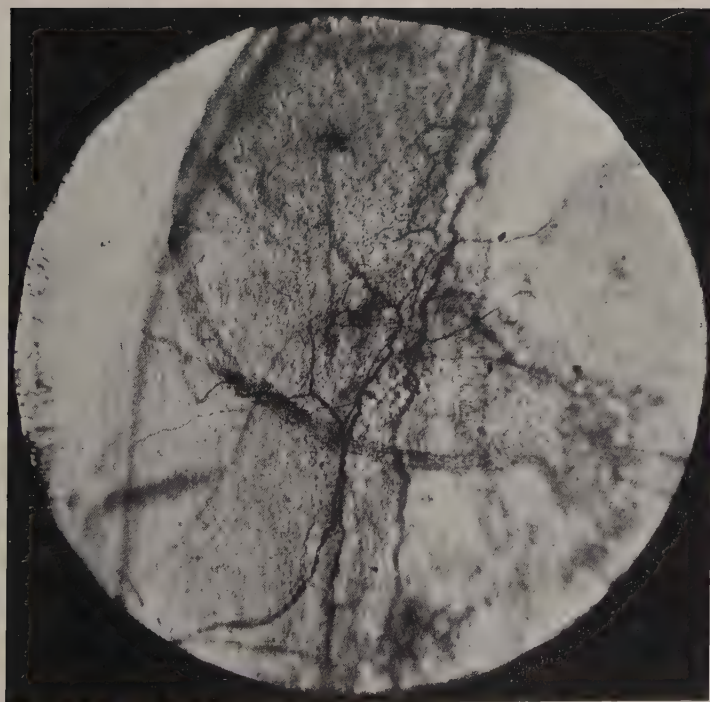
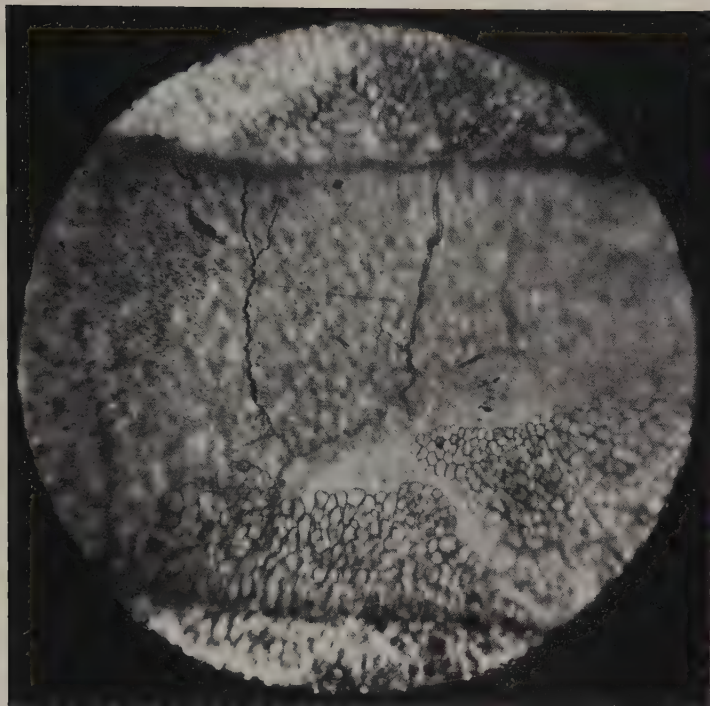


Figure 13.

Freely terminating nerves of artery of rabbit's ear.

The vessel runs downwards in the field of vision; upwards to the right a nerve passes in upon the vessel and there divides dichotomously; none of the branches, however, end upon the vessel, but only in its vicinity; the left branch is seen leaving the artery to end in the surrounding fatty tissue; the nerve running along the left side of the artery, however, belongs to the *plexus adventitialis* of the vessel itself.

The preparation stained and fixed as described in p. 46.

1½ year after preparation the stain was unchanged.

II/199.

Figure 14.

Nerves upon artery of mucous membrane of rabbit's bladder.

The bundles of the *plexus adventitialis* are distinctly seen running longitudinally; on the other hand the meshes of the combined *rete interlamellare* and *rete musculare* are perhaps merely suggested rather than really seen — in some places at any rate they lie in the plane of the photograph.

The preparation stained and fixed as described in p. 46.

½ year after preparation the stain was unchanged.

II/243.

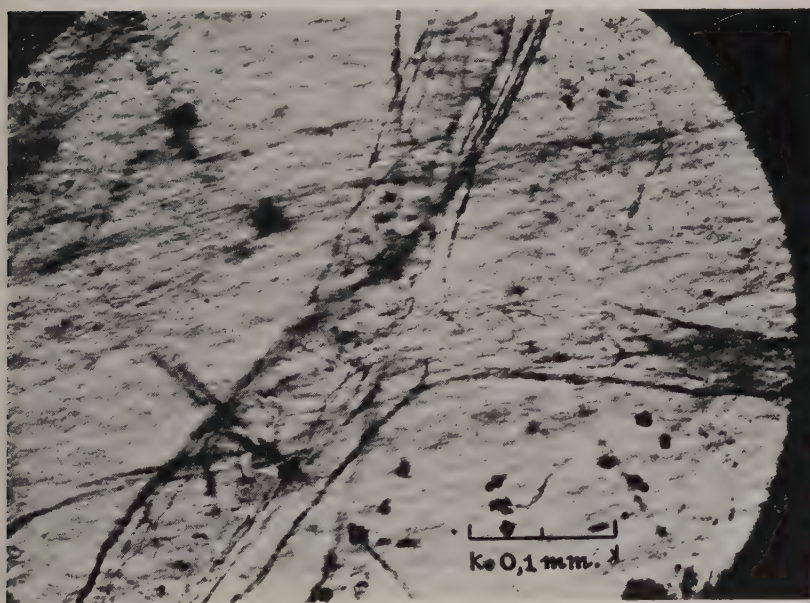
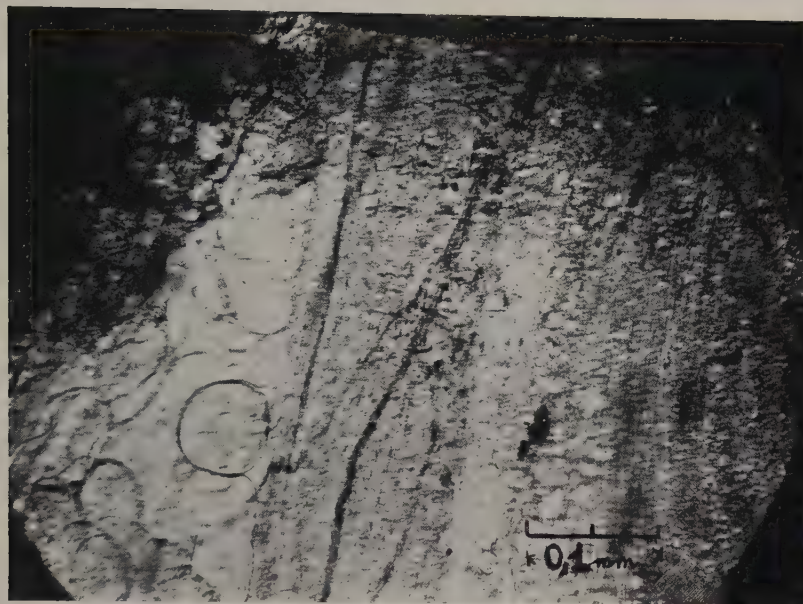


Figure 15.

Peripheral, sympathetic ganglion cell upon precapillary artery of pararenal tissue (rabbit).

The artery comes from the right, lower, corner of the picture; divides at about the middle of the picture into two capillaries; just at the point of division lies a typical, sympathetic ganglion cell with a large, vesicular nucleus; the cell is by 4 processes united with the reticular nerves of the vessel — or forms these.

The preparation stained and fixed as described in p. 46.

$\frac{1}{2}$ year after preparation the stain was unchanged.

II/252.

Figure 16.

Capillary nerves from the pararenal tissue (rabbit).

The capillary runs obliquely across the field of vision, surrounded by the nerves, which at about the middle of the picture are connected by an anastomosis running transversely across the capillary; downwards to the right on the lower nerve a nucleus of *Remak*.

The preparation stained and fixed as described in p. 46.

$\frac{1}{2}$ year after preparation the stain was unchanged.

II/254.

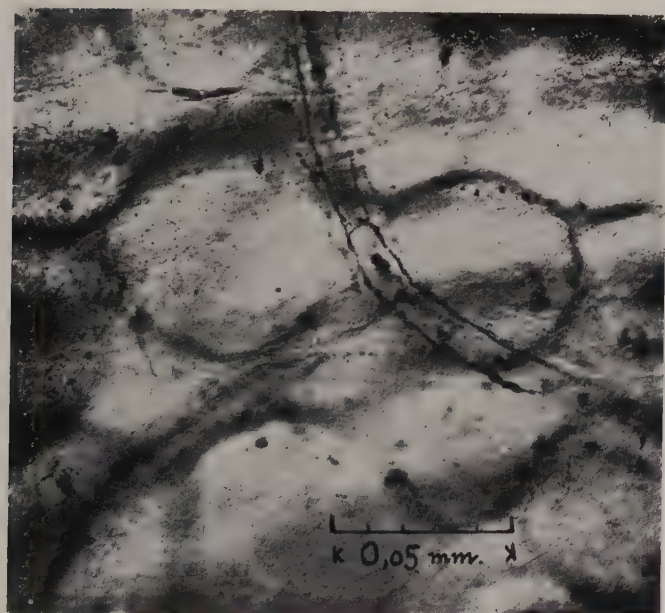
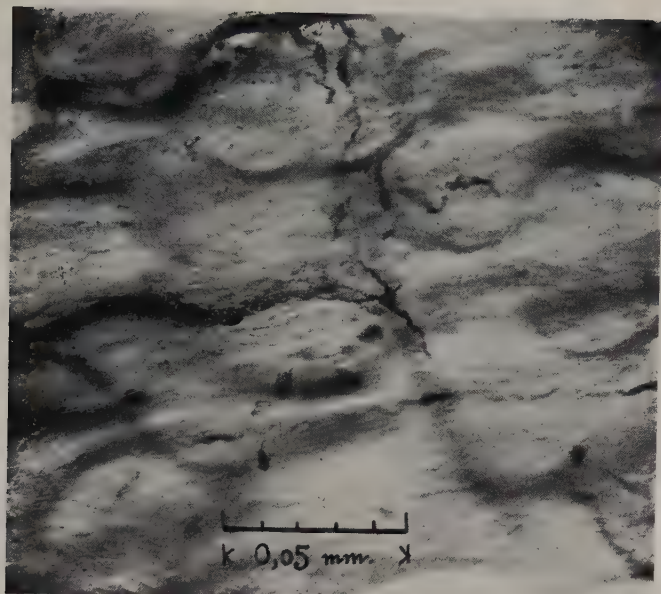


Figure 17.

Freely ending (sensory) nerves upon the femoral vein of the rabbit.

The nuclei of the muscle-cells show through; a larger medullated nerve comes from the right and divides into branches at a peripherally always increasing angle.

The preparation stained and fixed as described in p. 46.

One year after preparation the stain was quite lost.

II/77.

Figure 18.

Plexus adventitialis from the posterior tibial artery of man.

The angle of a mesh formed of non-medullated nerve-bundles; crossing the superior bundle a small artery (*vas vasorum*) in this place only perceptible by its nerves, one upon each side of the vessel — still further upwards in the preparation the nuclei of the muscle-cells were stained and the lumen filled with red corpuscles.

The preparation stained and fixed as described in p. 46.

$\frac{1}{2}$ year after preparation the stain was unchanged.

I/348.

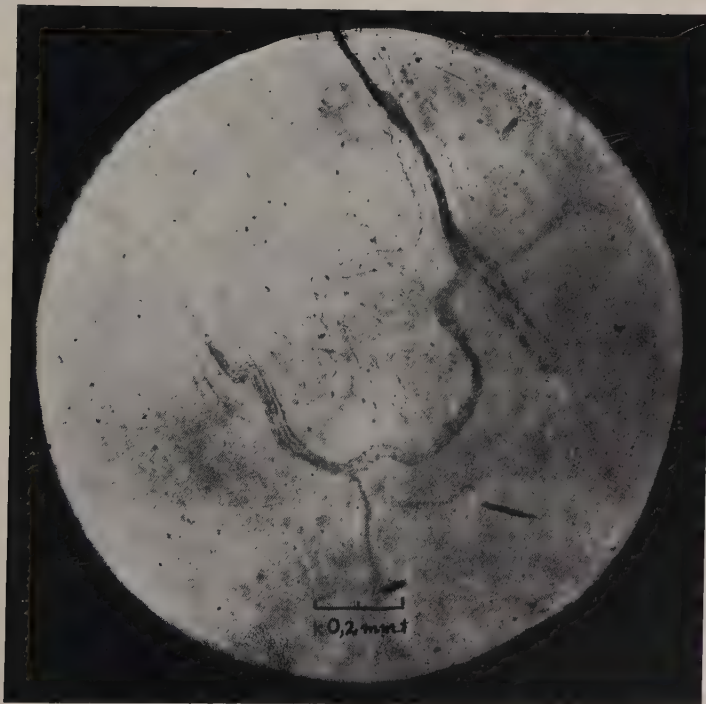
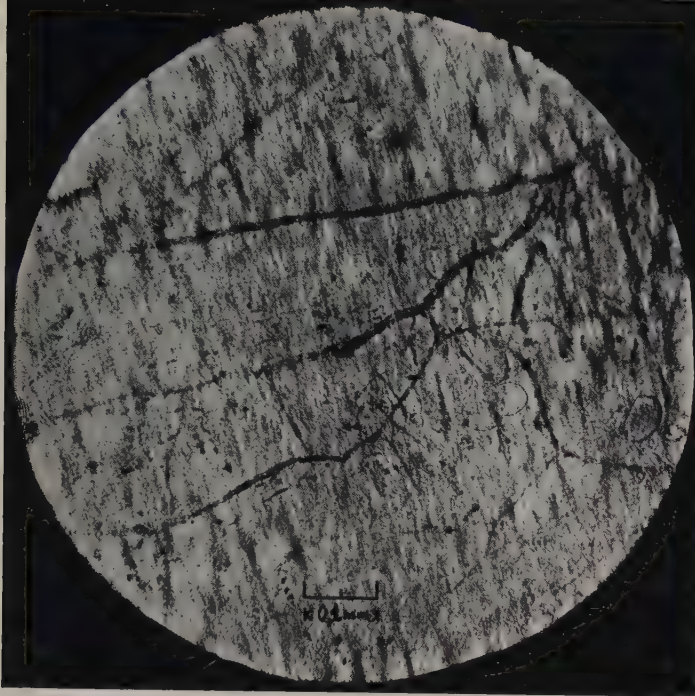


Figure 19.

Rete interlamellare from the art. profunda femoris of man.

The fibres of the large-meshed net are seen; the "granular-protoplasmic" appearance of the nerves may be recognised. Deeper down the nuclei of the muscle-cells are faintly suggested.

Compare fig. 20!

Figure 20.

Rete musculare from the art. profunda femoris of man (the same preparation and the same place in the preparation as fig. 19, the only difference being that the micrometer-screw has been lowered a little).

The thinner and more varicose fibrils are seen running over and under the individual muscle-cells, whose nuclei are deeply stained; the neuro-fibrils are perhaps faintly suggested outwards to the right in the picture.

The preparation stained and fixed as described in p. 46.

$\frac{1}{2}$ year after preparation the stain was unchanged.

I/205.

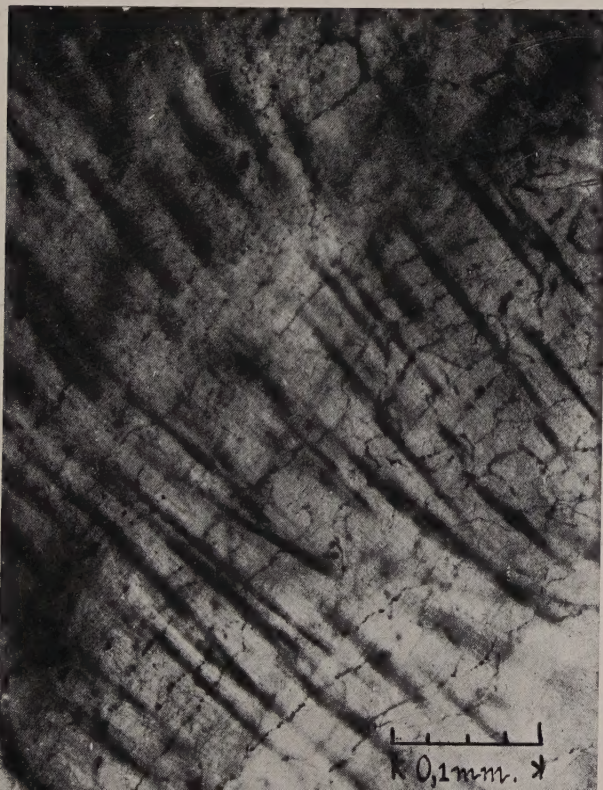


Figure 21.

Rete musculare from the art. femoralis of man.

In this preparation the muscle-cells are unstained, consequently the arrangement of the nerve-net may be better seen.

The preparation stained and fixed as described in p. 46.

$\frac{1}{2}$ year after preparation the stain was passable, but distinctly faded.

I/203.

Figure 22.

Drawings (a, b, d free hand, c by means of Abbe's apparatus).

- a & b) Nuclei of *Rouget* cells from the capillaries of the mucous membrane of the *rabbit's* bladder; the nerve seemingly divides into several thin fibrils, which, however, probably all reunite on the other side of the nucleus (*see p. 69*).
- c) A small artery (precapillary) from the subcutis of the *human* leg; the muscle-cells are stained, lie gradually more and more obliquely upon the vessel; bundles running longitudinally: "*plexus adventitialis*"; originating in this plexus a neurofibril, which touches the muscle-cells opposite their nuclei, *being obliged to cross the vessel several times in order to do this*.
- d) Encapsuled "*sensory*" end-corpuscle from the adventitia of the human *art. femoralis*. The corpuscle is 0,15 mm. long.

II/317 & I/207 & I/233.

